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ADENOMA AND CARCINOMA OF THE THYROID GLAND*

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STATISTICS on the incidence of cancer in nodular goiter are totally unreliable because all such statistics are based on the selected group of patients whose goiters are removed. Since most patients with small benign nodular goiters are not operated upon and since most patients with true carcinomas sooner or later are operated upon, it is obvious that statistics based on surgical pathology are not representative of the over-all incidence of cancer in nodular goiter.

The incidence of nodular goiter varies from place to place and increases with advancing age. In the Great Lakes area, for example, about 5 per cent of the population at large and a much higher percentage of women over fifty have palpable nodules in the thyroid gland. At autopsy in people beyond the age of fifty, it is almost impossible to find a normal thyroid gland, and the vast majority of women of this age have involutionary nodules of greater or lesser size. From the pathologic standpoint, therefore, nearly all women over fifty in the Great Lakes area have nodular goiters, and from the clinical standpoint, nearly 10 per cent of them have palpable nodules in the gland.

INCIDENCE OF THYROID CANCER

Many frightening statistics on the incidence of thyroid cancer in nodular goiters have been published, and it has been stated that 11 per cent of nontoxic multinodular goiters and 24 per cent of all nontoxic "solitary adenomas" prove to be malignant.[1] These figures, of course, refer only to the incidence of cancer in the nodular goiters that are removed and do not consider the thousands of people with small nodular goiters who are not operated upon. If fallacious reasoning led one to apply the incidence of cancer in surgical specimens to the population at large one would come to the absurd conclusion that in a Great-Lakes city like Cleveland, with 1,000,000 inhabitants, 50,000 of whom have clinically detectable nodules in the thyroid gland, there would be at least 4000 people walking the streets with thyroid cancer. Since cancer of the thyroid gland stands seventeenth in the list of cancers causing death and is only one thirty-seventh as common a cause of death in women as cancer of the breast,[2] such figures are erroneous. No true estimate of the incidence of thyroid cancer can be made unless no operations are performed for nodular goiter, a large population group is followed to death, and the thyroid glands of all are examined at autopsy.

TYPES AND NATURAL HISTORY OF THYROID CANCER

Twenty-five years ago, when Allen Graham was making his historic studies of cancer of the thyroid gland, the incidence of papillary cancer of the gland at the Cleveland Clinic was reported as being only 16 per cent of the total. Today, at the same institution, 60 per cent of these carcinomas are papillary. How can this change in type be accounted for?

The natural history of papillary cancer of the thyroid gland is one of extremely slow growth. Often, there is no apparent enlargement of the thyroid tumor during periods of ten or twenty years of observation, and frequently these tumors remain small, sclerosed or calcified for indefinite periods. The same slowness of growth or high resistance of the host often applies to the lateral cervical metastases of these tumors, which may also remain small and localized over periods as long as twenty-seven years.[3] It is therefore possible that many patients in the period before 1925 went through life with low-grade thyroid carcinomas that were interpreted either as harmless adenomas or, if they had metastasized, as tuberculous lymph nodes. This theory is further substantiated by the fact that the average age of patients operated on for papillary cancer in the 1920's was over fifty whereas today it is only thirty. Also the average papillary cancer in the 1920's was a large tumor, 6 to 8 cm. in diameter, whereas today they are small, most of them being only 1 to 3 cm. in diameter.

The preceding data suggest that in recent years patients with papillary cancer of the thyroid gland are operated on much more often and much earlier than formerly, and it also appears that before 1930, when removal of thyroid nodules and biopsy of enlarged cervical lymph nodes were not as common

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as today, many patients lived out their natural lives with low-grade papillary cancer and were never operated on.

Careful examination of all thyroid glands removed for either Graves' disease or multinodular goiter or at autopsy shows that 1 in 200 contain a small sclerosing papillary carcinoma,[3] 1 cm. or less in diameter, that was not palpable before operation.[4] Although some of these lesions may "grow up" into clinical papillary carcinomas, their presence in a specimen removed for other reasons should not excite alarm, because if the gross tumor is removed completely metastasis or recurrences are not observed. Yet today, with the widespread fear of cancer shared by both physician and patient, many patients with such lesions are subjected to the most radical and mutilating surgical dissections and what remains of their necks is treated with tremendous doses of roentgen rays. I believe that this needless mutilation in this group of papillary carcinomas causes more disability than it has prevented.

The second great group of thyroid cancers are the nonpapillary carcinomas, which fortunately are uncommon before middle age. Most of them are highly undifferentiated tumors of the greatest malignancy that almost invariably run a rapidly fatal course undeterred by the most radical attempts at excision or by radiation or isotope therapy. Patients with these cancers give a short and typical history of rapid growth, and 80 per cent of them have no knowledge of a pre-existing benign goiter. Most of these patients show involutional change in the noncancerous parts of the gland, but these changes are no different from those found in this age group in the population at large.

All nonpapillary carcinomas are not as malignant as the undifferentiated tumors. There is a small group of angioinvasive adenomas that are so benign in their histologic appearance and clinical behavior that invasion of blood vessels by tumors cells or the observation of a distant metastasis is all that distinguishes them from the benign type. Between these tumors and the undifferentiated variety stands a small group of adenocarcinomas of intermediate malignancy.

Since the true adenocarcinomas are fatal in about 50 per cent of cases even when treated by the most radical operations, and since papillary carcinomas are rarely fatal if the primary tumor is removed completely at the first operation, it is important, for prognostic reasons, to differentiate the true nonpapillary adenocarcinomas from the alveolar variants of the papillary cancer. The latter are just as benign in their behavior as the true papillary form and are distinguished from the true adenocarcinoma by a benign clinical course, by the finding of papillary areas in the tumor or its metastases and by the fact that they occur most commonly in patients under the age of forty. Tumors of high malignancy seldom occur in patients under forty. On rare occasions medullary tumors[5] of moderate malignancy occur in younger patients.

From the preceding summary of the clinical behavior of the various types of thyroid cancer, it is apparent that those that occur in the older age groups, unless they are typical papillary carcinomas or the rare angioinvasive adenoma, tend to be highly malignant, whereas the vast majority of tumors that occur frequently in patients under forty behave like papillary carcinomas and are of the lowest order of malignancy even when the histologic arrangement is predominantly alveolar. Clinical as well as morphologic evaluation of these tumors is necessary before a balanced program of therapy can be planned.

Treatment of Multinodular Goiter

Multinodular goiter is characteristically a disease of the involutional period and occurs predominantly in patients over forty years of age. It is rare for such involutional changes to appear in children or young adults.

Today, with the availability of antithyroid drugs and radioactive iodine, the problem of hyperthyroidism is easily solved and it is not necessary to worry about removing goiters prophylactically lest they become toxic. Serious consideration, however, should be given to the question of malignancy in nodules in the thyroid gland.

There are several reasons why all multinodular goiters cannot be removed to prevent the ultimate development of cancer; despite the fact that multinodular goiter is common, true highly malignant thyroid cancer is very rare; 80 per cent of the highly malignant carcinomas arise without any history of pre-existing goiter; and there is no demonstrable causal relation between nodular goiter and the relatively common papillary cancer. For these reasons and because of the much greater frequency of cancer in the breast or cervix, a woman with a multinodular goiter would probably be better protected against the development of fatal cancer by removal of a normal-appearing breast or cervix than by partial removal of a multinodular goiter. Nevertheless, all nodular goiters in which the history or consistence of the tumor is such as to suggest that cancer could exist at the time of examination should be removed. The situation is much as in cystic mastitis: it is suspected that the incidence of cancer of the breast is a little higher in diffusely nodular breasts than in those which are not, but this slight increase in incidence is not sufficient to indicate bilateral simple mastectomy in all women with nodular breasts — instead of removing these breasts, one merely excises such nodules as are considered suspicious of cancer. Similarly, in small multinodu-

lar goiters the routine prophylactic removal of all thyroid tissue is not recommended, but it is urged that all discrete tumors that could be cancer and all enlarging tumors be removed.

The Solitary Adenoma

The significance of a solitary nodule of the thyroid gland changes with the age of the patient. In patients over forty years of age, tumors that appear to be solitary are more likely to be dominant involutionary nodules in a multinodular goiter. But in people under forty, and particularly those under thirty, a solitary nodule of the thyroid gland is much more apt to be a true epithelial neoplasm. The significance of a nodule varies in the various age groups.

Youth. Nonpapillary carcinomas are rare under the age of forty, but even during these years an occasional atypical adenoma shows invasion of veins and must be classified as a low-grade cancer. Probably many of the solitary atypical adenomas that occur in younger patients ultimately invade veins and behave like malignant tumors, and for this reason and because of the frequency of papillary carcinoma in children and young adults, all solitary nodules in young patients should be removed.

Middle age. Between forty and sixty is a period in which involutionary nodules appear in the thyroid gland in increasing numbers, and in these years the presence of a solitary nodule is not as significant as in younger patients. Yet papillary carcinoma and low-grade nonpapillary cancers are relatively common in these years, and cannot always be differentiated clinically from benign adenomas. For these reasons, all discrete, firm, solitary tumors in middle-aged patients should be removed.

Patients over sixty. Many patients over the age of sixty have nodules that they have known about for fifteen or twenty years and that have not altered in size during this period of observation. Some of these are calcified and easily visible on x-ray examination. If the patient can be counted on to have given a reliable history, such tumors can be disregarded unless their hard consistence in the absence of calcification is suggestive of carcinoma. It is possible that some of these nodules are low-grade carcinomas, but experience has shown that tumors of this type grow so slowly that they would not be apt to cause difficulty during the life expectancy of a patient over sixty. The more malignant tumors enlarge rapidly and are almost always recognized clinically. For these reasons, routine "prophylactic" removal of all nodules in the thyroid glands of patients over sixty years of age is scarcely worth while, and since such nodules are so common it is quite possible that more patients would die as a result of "prophylactic surgery" than would have died of cancer if no operation had been performed. It seems wiser, in older patients, to reserve operation for nodules whose firm consistence or history of recent growth arouses the suspicion of existing carcinoma. "Prophylactic" operations designed to prevent the ultimate development of malignant change in the nodular goiters of patients over sixty years of age are probably of little value.

Type of Operation for Thyroid Cancer

Since it appears that most thyroid carcinomas are malignant from the first and that the transition of a benign adenoma to a frankly malignant cancer is relatively rare, the operation for a solitary tumor of the thyroid gland should be an operation for cancer. As long as operations for thyroid nodules are regarded as "prophylactic" to prevent the ultimate development of cancer, these operations will be incomplete and followed by recurrences of cancer.

Removal of a nodule of the thyroid gland because of the possibility of cancer does not fulfill one's obligation to the patient if the nodule is merely "shelled out." Local operations of this type do not cure carcinoma. The minimal procedure should be removal of the entire nodule, intact, with a wide zone of surrounding normal thyroid tissue. Total removal of the affected lobe and isthmus is still better, and much safer because many of the papillary carcinomas infiltrate diffusely or are multicentric. Often, in diffusely infiltrating lesions, total thyroidectomy is the best treatment.

Problems Peculiar to Papillary Cancer

Distant metastasis and extensive invasion of surrounding structures are distinctly uncommon in papillary cancer of the thyroid gland except in cases in which an incomplete primary operation has been performed and the tumor or its cervical metastases cut into. When the tumor is cut across the local recurrences tend to infiltrate muscle and implant themselves in the incision. The natural defenses of the body appear to have been destroyed, blood and lymph vessels are opened to invasion by tumor cells, and distant metastases as well as invasive local recurrences are common. Thus incomplete operations on low-grade thyroid cancers appear to predispose to the development of surgically incurable recurrences and metastases, whereas even long delays in the treatment of an undisturbed low-grade papillary carcinoma do not often render the lesion inoperable or incurable by eventual radical surgical attack. For this reason, it is safer not to treat papillary cancer of the thyroid gland at all than it is to treat it by limited operations in which the primary tumor or its individual metastases are incompletely excised.

Despite the fact that cases have been reported in which even low-grade thyroid cancers have been implanted in the skin by biopsy,[8] surgeons continue to biopsy thyroid tumors at the time of operation. These surgeons would not dream of cutting into a grossly involved axillary lymph node or a primary breast tumor at the time of radical mastectomy;

yet they do not hesitate to contaminate a thyroid wound by inserting hemostats or clamps into thyroid tumors or excising pieces of them for microscopical examination. Since the ideal operation for both benign and malignant tumors is total extirpation of the involved lobe and since this operation can be done just as safely and easily as the tumor can be enucleated, there should be no excuse for biopsy except possibly in rare cases when both lobes are involved and the question of total thyroidectomy or the differentiation of infiltrating cancer from thyroiditis arises.

Inadequacy of Standard Block Dissection

The problem of thyroid carcinoma has been taken over in recent years by the "cancer surgeons," who are strong advocates of a standardized radical neck dissection in all cases of cancer of the head, neck and thyroid gland. These surgeons have applied to the thyroid gland the conventional block dissection used in the treatment of squamous-cell cancer of the head, apparently disregarding the fact that the zone of metastasis in thyroid cancer is totally different from that of cancer of the mouth. They advocate the removal of the sternomastoid muscle and do not hesitate to sacrifice the eleventh nerve despite the fact that these nerves and muscles are seldom if ever involved by extension or metastasis of papillary carcinoma except in cases in which tumor has been implanted by an inadequate primary operation. Nor do they hesitate to sacrifice the inframandibular branch of the facial nerve so that they can have access to the submaxillary triangle although this triangle is rarely involved by metastases from papillary cancer of the thyroid gland. They do not hesitate to subject their patients after operation to as much as 6000 r of "prophylactic" radiation despite the fact that there is no statistical evidence that the papillary cancer is often sensitive to x-rays or that patients in whom tumors appear to have been removed completely do any better when given such destructive doses of irradiation. If these procedures were being carried out on old men, there would be little to lose by such treatment, but unfortunately the average age of patients with papillary cancer is thirty, and the majority of cases occur in young girls.

The conventional radical neck dissection is ineffective in extirpating the areas in which metastasis from papillary cancer is most common and most serious. The commonest sites of metastasis are the retrothyroid or paratracheal lymph nodes, which lie behind the thyroid gland along the course of the recurrent nerve and descend in a chain into the superior mediastinum. Evans blue dye injected into the lateral part of the lobe of the thyroid gland at the time of operation can be seen to fill these lymph nodes first. The position of the nodes close against the posterior portion of the gland, around the recurrent nerve, and adherent to trachea and esophagus, makes them appear to be a direct extension of the primary tumor and often either causes the metastases to be overlooked altogether or results in needless sacrifice of a nerve that can be dissected free. The conventional radical neck dissection does not remove these lymph nodes.

A second group of lymphatics commonly involved extends downward with the thyroidea ima vessels from the isthmus and the lower central portion of the thyroid lobes to the anterior superior mediastinum. This group of lymph nodes, like the mediastinal extension of the retrothyroid nodes, is surrounded by a fatty envelope and usually can be removed en bloc. The conventional radical neck dissection avoids these nodes.

A third group of lymph nodes frequently involved in diffuse cancers and in those located in the isthmus is found above the thyroid gland in the midline. This includes the group of delphian nodes described by Cope and located just above the isthmus, and a chain of similar nodes along the thyroglossal tract extending upward as far as the hyoid bone. These nodes are not included in the conventional neck dissection.

Contralateral involvement of lower cervical lymph nodes is common in cases in which there is extensive unilateral metastasis or the tumor involves the isthmus. Diffuse involvement of the thyroid gland or multicentric areas of papillary cancer occur in more than 10 per cent of all cases and require total thyroidectomy and thorough exploration or dissection —or both—of both sides. Contralateral exploration or dissection is difficult through the incision of the conventional operation for neck dissection.

Operation for Papillary Cancer

Experience has shown that the metastases of papillary cancer are embolic and —unlike those of cancer of the breast—do not diffusely infiltrate the lymphatics and tissues around the lymph nodes. Fortunately, therefore, the principle of block dissection in continuity with the primary tumor need not be applied to papillary cancer, and the metastatic nodules can be excised in groups surrounded by their envelopes of fatty and areolar tissue. Individual excision of nodes is never recommended except when their proximity to important structures, like the recurrent nerve, necessitates this type of dissection.

I have never seen an inoperable recurrence of papillary cancer of the thyroid gland except in cases in which tumor has been implanted or disseminated by an initial, incomplete operation or biopsy. The inoperable recurrences after inadequate operations have been central in location, occurring in the thyroid or retrothyroid area or in the superior mediastinum, and none of them in the lateral cervical region. The critical regions of local recurrence and

metastasis include the trachea, the esophagus, the area of the retrothyroid nodes and the superior mediastinum (Fig. 1), and yet their importance is often not even mentioned in authoritative reviews of the lymphatic spread of cancer.[7] Nor has enough emphasis been laid on the fact that the lateral cervical lymph nodes that are commonly involved are apt to lie deep to the carotid artery and vagus nerve and are not removable in continuity with the jugular block.

Since the conventional block dissection does not attack or even properly expose the most important zones of metastasis of papillary cancer, what incisions should be used?

For unilateral lesions involving the upper pole, the primary zone of metastasis is the lateral cervical region, and a satisfactory dissection and good cosmetic result can be obtained by complete removal of the isthmus and affected lobe of the thyroid gland and the nodes of the jugular and carotid chains. This can be accomplished through an anterior sternomastoid incision in which the muscle, the recurrent laryngeal, vagus, eleventh and seventh nerves are preserved. The retrothyroid and mediastinal lymph nodes can also be explored through this incision and removed if grossly involved. Eckert and Byars[8] reported a posterior cervical incision whose lower portion is curved forward transversely, giving good exposure and a fairly satisfactory cosmetic result.

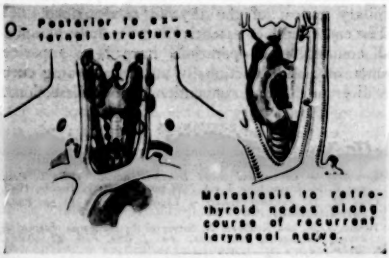

FIGURE 1. *Diagram of Common Zones of Lymph-Node Metastasis from Cancer of the Thyroid Gland.*

In more extensive lesions in which bilateral involvement is demonstrable or suspected, it is often necessary to do a total thyroidectomy. In such cases, it is always undesirable to divide the thyroid isthmus because the tumor may be infiltrating the gland and may be implanted if it is cut into. When the involvement is bilateral, neither the cosmetic results nor the exposure are as good through lateral cervical incisions as through a high, wide thyroidectomy incision that extends backward far into the posterior triangle on each side.

The flaps of this wide incision can be dissected up as far as the hyoid and downward to the clavicles. The lateral extensions give access to the posterior triangles and the brachial plexus. The exposure of the thyroid gland, the mediastinum and the midline and retrothyroid lymph nodes is excellent. Both sides can be explored and dissected simultaneously. The only nodes not accessible through this type of transverse incision — those of the submaxillary triangle — are rarely involved in thyroid cancer. All other nodes can be removed in groups in their surrounding fatty tissue, with or without sacrifice of one of the jugular veins for the sake of convenience. The sternomastoid muscles can be divided low and resutured at the completion of the operation if exposure of the carotid nodes is not adequate. The cosmetic result is nearly as perfect as that after conventional thyroidectomy.

Postoperative radiation is neither necessary nor desirable in cases in which the primary operation has been complete. In a consecutive series of 24 cases in which there had been no previous operation on the thyroid gland, 20 patients had metastases in cervical lymph nodes, and all but 1 lesion were operable (Table 1). In the inoperable case, biopsy only was performed, and although the tumor was predominantly papillary its growth activity appeared to be higher than usually seen in papillary tumors; it is likely that other areas would have shown undifferentiated cancer. This patient died promptly despite irradiation. The other 23 patients have been followed for three to fifteen years. At present there are no local recurrences, and the only distant metastasis was in a case in which the tumor implanted itself in skin after a needle biopsy necessitated by the patient's initial refusal of operation. In several patients early in the experience with this disease recurrences developed in the midline contralateral or posterior triangle outside the field of the primary operation, but all these have been controlled by small secondary operations and the patients have remained well for many years. Since careful but extensive operations planned to remove all the primary tumor and all the nodes to which

TABLE 1. *Results in 24 Cases of Papillary Cancer.**

No. of Cases	Result
20	Survival without recurrence 3 to 15 yr. (average, 7.1 yr.)
2	Death from other causes without recurrence (2 yr. and 12 yr. after operation)
1	Survival with distant metastasis (4 yr.)
1	Death from cancer (1 yr.)†

*In 20 cases there was involvement of regional lymph nodes.
†A biopsy only was performed in this case.

thyroid cancers most commonly metastasize are attended by excellent cosmetic results and by a higher incidence of control of cancer than has been reported after conventional block dissection and x-ray therapy, there appears to be no indication for the more disabling and mutilating therapeutic procedures that are at present in vogue in the primary treatment of papillary cancer of the thyroid gland. In cases in which the cancer has been disseminated and implanted by previous incomplete operations, block dissections with removal of muscles is necessary.

Summary and Conclusions

Statistics on the incidence of cancer in nodular goiter are unreliable because they are based on the selected group of patients whose goiters are removed and do not represent the true incidence in the population at large.

Removal of all multinodular goiters cannot be regarded as a prophylactic measure to prevent the ultimate development of cancer because multinodular goiter is extremely common and true highly malignant cancer of the thyroid gland is very rare, 80 per cent of the highly malignant thyroid carcinomas arise without any history of pre-existing goiter, and there is no demonstrable relation between nodular goiter and the relatively common papillary cancer of the thyroid.

All discrete thyroid tumors that are firm and that arouse suspicion of existing cancer should be removed whether they occur as the only palpable nodule or as a part of a multinodular goiter.

Nodules that appear in patients over the age of forty and seem to be solitary are usually dominant involutionary nodules in a multinodular goiter.

In patients under forty a solitary nodule is apt to be a true epithelial neoplasm, and the incidence of cancer is high. Most cancers of the thyroid gland in patients under forty are papillary and carry a good prognosis if an adequate operation is performed. Most thyroid cancers do not originate in adenomas but are cancers from the start.

Surgeons should view operations for removal of solitary nodules not as prophylactic measures to prevent the development of cancer but as therapeutic procedures designed to eradicate any cancer present. Even low-grade papillary cancers of the thyroid gland, if cut into, can be implanted and disseminated at the time of operation. Solitary tumors should be removed by total excision with a wide zone of surrounding tissue or better by total lobectomy, including removal of the isthmus.

The conventional block dissection of the neck is not an adequate operation for cancer of the thyroid gland and should be extended to include all the regional zones of metastasis. It should also be limited to the removal of cancer-bearing areas and should not, in most cases, include the unnecessary sacrifice of the sternomastoid muscle.

An effective and nonmutilating operation for papillary cancer of the thyroid is described.

The end results of extensive but carefully planned and nonmutilating operations have been superior cosmetically and functionally and in affording cure of cancer to those of conventional block dissections.

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PLATELET ANTIBODY TESTS IN THE DIAGNOSIS OF PURPURA*

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PURPURA is a heterogeneous group of diseases with a single common denominator of spontaneous extravasation of blood. Classically, the purpuras are divided into two major classes: symptomatic and thrombopenic, depending on the presence or absence of a normal platelet count. The former is generally considered of allergic origin. Madison[1] has advanced the concept that allergic factors may account for the vascular permeability that is present in both types of purpura. Yet the clinical manifestations are sharply different, since thrombopenic purpura presents the added problem of platelet deficiency, with its resultant coagulation defect and incomplete clot retraction.

The present communication deals solely with thrombopenic purpura. This type of purpura is subdivided into primary (idiopathic) thrombopenic purpura and secondary thrombopenic purpura. The latter is thought to be secondary to some other disease entity that has involved the bone marrow, liver or spleen — for example, leukemia or Hodgkin's disease. The primary form has been ascribed to humoral inhibition of platelet formation, to increased rate of platelet destruction and to combinations of these two factors.

Recently, a significant advance in knowledge of the basic etiologic mechanisms of thrombopenic purpura has been made with the discovery that immune reactions of antigen-antibody type underlie many cases of thrombopenic purpura, and that the thrombopenic purpura of "hypersplenism" is not always due to a single mechanism but may be secondary to both immune factors and filtration effects.

An immune mechanism as the etiologic factor in thrombopenia was first suggested almost a half century ago, when Marino,[2] in 1905, produced an antiplatelet antibody by injection of rabbit platelets into guinea pigs. A few years later, Ledingham[3] caused experimental purpura in animals by the administration of antiplatelet antiserums. Tocantins,[4] in 1935, used such antiplatelet serums to study the role of platelets in bleeding phenomena. Yet surprisingly little extension of these fundamental studies into clinical states of thrombopenia was made until Evans,[5] in 1948, presented evidence of a thrombocyte-agglutinating factor in the serum of patients with idiopathic thrombocytopenic purpura, and Ackroyd,[6] a year later, demonstrated platelet agglutinins in the thrombopenia secondary to Sedormid sensitivity. The theory that a circulating antibody was responsible for thrombopenia was dramatically proved shortly afterward by Harrington et al.[7] by cross transfusion between purpuric patients and normal volunteers.

Such a concept may be of considerable significance to the clinician faced with the diagnosis and treatment of thrombopenic purpura. Cases secondary to antigen-antibody reaction give promise of responding to the administration of ACTH and cortisone. Cases with deficient platelet production secondary to bone-marrow displacement or aplasia do not give as much promise of responding to these hormones. Moreover, with the recent introduction of platelet transfusions from either preserved platelets[8] or platelet-rich, polycythemic blood,[9] another therapeutic weapon is available for the treatment of thrombopenia. Such transfusions can be of significant clinical benefit in cases in which thrombopenia is due to bone-marrow invasion or aplasia. Yet such transfusions usually are not of clinical benefit in patients in whom a significant titer to antiplatelet antibody exists.

If one is faced with the necessity of differentiating purpuras that are due to an antibody from those that are not, some simple in vitro test for the demonstration of platelet antibodies must be devised. Several tests have been under study and have been reported from different laboratories.[5, 10, 11-13] Most of the tests are designed to demonstrate platelet agglutinins. The purpose of at least one[11] is to screen for both platelet agglutinins and platelet lysins (if, indeed, lysins exist). Although it will take many years of study and extended statistical survey to determine properly the incidence of antibody-induced thrombopenic purpura, sufficient data have been acquired through the routine use of one simple in vitro test to be of significant help in the treatment and clarification of this confusing disease.

METHOD

The test consists of an in vitro mixture of preserved platelets, human complement and unknown serum. The mixture is incubated at 37°C. and studied for quantitative change in total count at the end of forty-five and ninety minutes. Morphologic alteration or the presence of clumping, or both, is also recorded. A normal control serum is tested at the same time as the unknown, to minimize errors

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that could arise from variation in antigen (preserved platelets). If the normal control shows greater than 5 per cent fall in platelet count at ninety minutes, the test is repeated with a different source of plate-

TABLE 1. *Fall in Platelet Count of Normal Serum.*

No. of Tests	Range at 45 min.	Range at 90 min.	Average at 45 min.	Average at 90 min.
	%	%	%	%
72	0–5	0–5	1	2
32	1–5	2–6	4	5
Total 104			2	3

lets and complement. The results are expressed in simple terms of a positive or negative test and no gradation of severity is made. The serums are used full strength without titration. Plasma may be used instead of serum, which, however, gives more uni-

TABLE 2. *Fall in Platelet Count of Serum from Patients with Nonthrombopenic Purpura.*

No. of Cases	Range at 45 min.	Range at 90 min.	Average at 45 min.	Average at 90 min.
	%	%	%	%
4	1–4	1–4	2	2

form results. This is believed to be due to the variation in amount and type of anticoagulant used in the preparation of plasma. An excess of metal complexing agent may interfere with the reaction between test platelet and serum, and if ethylene-diamine-tetra-acetate is used the plasma may even become anticomplementary, as noted by Harrington et al.[13]

MATERIALS

Platelet

The antigen used for the test consists of a standard supply of preserved platelets. The method for their preparation, which is reported elsewhere,[9] consists of storage at 4°C. in a gelatin*-acetate medium. The platelet count of the gelatin suspension for this test averages 400,000 to 500,000 per cubic millimeter. It is of interest that the platelet stock should be relatively free of both red and white cells (less than 500 red cells and 300 white cells per cubic millimeter) to avoid the formation of reticulum strands during the incubation of platelets and serums; 1 cc. of preserved platelets is warmed to

TABLE 3. *Fall in Platelet Count of Serum from Patients with Idiopathic Thrombopenic Purpura.*

No. of Tests	Range at 45 min.	Range at 90 min.	Average at 45 min.	Average at 90 min.
	%	%	%	%
Negative 9	1–6	0–6	3	3
Positive 9	3–28	12–38	17	24

37°C. for five minutes and added to a silicone-coated 0.7-cc. Wintrobe hematocrit tube. This is placed in a clinical centrifuge at room temperature and run at half speed for ten minutes. The supernatant material (approximately 0.8 cm.) is removed. The remainder (0.2 cm.), which contains concentrated platelets is resuspended with a silicone-coated Wintrobe pipette. This is equal to 0.14 cc. and is sufficient for two tests. The two aliquots of 0.07 cc. are added to separate 4-cc. vaccine vials in which the test is to be carried out.

TABLE 4. *Effect of Therapy or Clinical Improvement in Primary Idiopathic Thrombopenic Purpura.*

Patient	Fall in Count at 45 min.	Fall in Count at 90 min.	Test for Circulating Antibody	Remarks
	%	%		
T. C.	4	5	Negative	Acute purpura
P. (L. K. D.)	3	3	Negative	Congenital purpura
P. (L. K. D.)	4	5	Negative	Same case after 4 platelet transfusions
Baby D.	6	19	Positive	Acute purpura
M. D.	5	4	Negative	Recurrent purpura 25 yr. now in remission
Mrs. S.	16	28	Positive	Acute purpura
K. (J. B.)	26	38	Positive	Acute purpura
G. D.	18	19	Positive	Acute purpura on cortisone therapy
J. W.	5	3	Negative	Acute purpura
J. W.	3	5	Negative	Same case on cortisone therapy
Z. (L. K. D.)	3	12	Positive	Idiopathic purpura; patient unable to receive platelet transfusion.
Z. (L. K. D.)	2	10	Positive	Same case on cortisone therapy
Bethel Clinic	4	0	Negative	Chronic purpura 1 yr. after splenectomy
W. O.	20	18	Positive	Acute (recurrent) purpura
E. (L. K. D.)	1	2	Negative	Idiopathic purpura after splenectomy
A. P.	28	34	Positive	Acute purpura
R. S. (H.)	17	24	Positive	Acute purpura
R. B. (H.)	3	3	Negative	Idiopathic purpura

Complement

A sample of serum (derived from the same normal donor as the original platelets) is filtered with No. 50 Whatman pads, divided into 0.2-cc. aliquots and stored at −40°C. This sample serves as a source

*Decalcified by passage through IRC-50 carboxylate resin at pH of 7.2.

of complement and is subject to the variation in complement level that exists in normal blood donors. Before use, it is warmed to 37°C. and diluted 1:32; 0.05 cc. of this material is then added to the vaccine vials containing platelets as noted above.

Serum

Serum for the test is collected as whole blood into chemically clean, sterile test tubes. It is allowed to clot and is then stored at ice-box temperature for transport or until the serum has been separated — 0.15 cc. of serum is sufficient for a test, but to facilitate handling, at least 1 cc. should be obtained. After separation from the red-cell clot, the serum is passed through XE 128 resin* (0.1 cc. of resin per cubic centimeter of serum) in the bottom of a tuberculin syringe for adsorption of SPCA. It is then centrifuged until clear of particulate barium,† and the supernatant serum is stored in a deep freeze. If the serum is to be tested within a week or two, standard ice-box temperature is satisfactory; 0.15 cc. of serum is added to each of the silicone-coated vaccine vials containing platelets and complement as noted above.

Test

A single specimen of unknown and a split specimen of normal control are run simultaneously. The vaccine vials are placed in a 37°C. water bath. An immediate platelet count is drawn from each vial, and a fresh cover slip preparation is rimmed with vaseline and incubated at 37°C. The platelet counts must be made by the method of Brecher and Cronkite[14] utilizing 1 per cent ammonium oxalate, red-cell pipettes and phase microscopy. No other platelet-counting method proved sufficiently accurate for this test. To regulate the accuracy of counts further, only the same cover glasses and the same sides of the same counting chambers are used for the three successive counts on each aliquot. Because the results of the test reflect relative change in total count rather than absolute numbers of circulating platelets, the accuracy of the method is sufficient for reproducible results. At the end of forty-five minutes, platelet counts are drawn and the mixtures reincubated for another forty-five minutes. Final counts are then made, and a repeat set of

TABLE 5. *Fall in Platelet Count in Thrombopenic Purpura Secondary to Radiation, Cancer, Bone-Marrow Aplasia and Toxic Drugs.*

No. of Tests	Range		Average	
	at 45 min.	at 90 min.	at 45 min.	at 90 min.
	%	%	%	%
Negative 25	0–5	1–6	2	3
Positive 1	14	10	14	10

TABLE 7. *Fall in Platelet Count in 7 Cases of "Hypersplenism."*

No. of Tests	Range		Average	
	at 45 min.	at 90 min.	at 45 min.	at 90 min.
	%	%	%	%
Negative 3	1–5	5–6	3	5
Positive 6*	2–5	10–19	3	15

*Includes 1 "positive" case that became "negative" 2 mo. after splenectomy.

TABLE 6. *Change in Platelet Count in Secondary Thrombopenic Purpura.*

Patient	Fall in Count		Test for Circulating Antibody	Cause of Purpura
	at 45 min.	at 90 min.		
	%	%		
W. N.	4	2	Negative	Chronic lymphatic leukemia
W. N.	2	5	Negative	Chronic lymphatic leukemia
S. M.	1	1	Negative	Mycosis fungoides
S. M.	2	3	Negative	Mycosis fungoides
K. (VA)	0	1	Negative	Hodgkin's disease
L. (VA)	0	2	Negative	Hodgkin's disease with thrombopenia
A. (VA)	3	5	Negative	Hodgkin's disease with thrombopenia
R. K.	1	3	Negative	Hodgkin's disease with thrombopenia
T.T.	3	6	Negative	Hodgkin's disease with pancytopenia, secondary to triethylene melamine
T. T.	3	6	Negative	Same case before treatment
A. K.	5	3	Negative	Reticulum-cell sarcoma with thrombopenia
A. K.	1	3	Negative	Reticulum-cell sarcoma with thrombopenia
M. D.	2	2	Negative	Lymphocytoma with thrombopenia
— B.	2	3	Negative	Radiation pancytopenia
L. R.	2	1	Negative	Radiation pancytopenia
S. D.	2	2	Negative	Hodgkin's disease with pancytopenia
— T.	5	5	Negative	Hodgkin's disease with hemolytic anemia
C. O.	1	1	Negative	Radiation pancytopenia
Mrs. O'D.	1	1	Negative	Myelofibrosis
L. G.	3	5	Negative	Acute leukemia
L. G.	5	5	Negative	Same case on cortisone therapy
J. T.	2	4	Negative	Acute leukemia
M. F.	3	2	Negative	Hodgkin's disease with thrombopenia
M. S.	2	3	Negative	Acute lymphatic leukemia with thrombopenia
J. McA.	2	3	Negative	Drug sensitivity
I. P.	14	10	Positive	Multiple myeloma with fulminating hemorrhage

*XE 128 (Rohm and Haas) carboxylate resin containing a physical suspension of barium sulfate.

†Care must be used to spin out all traces of barium to avoid nonspecific platelet agglutination.

cover-slip preparations is observed for morphologic change and microscopic clumping.

Results

Normal serum tested by this method gives either no fall in total count or less than 6 per cent fall during the ninety-minute period of incubation (Table 1). In 104 consecutive tests of normal control serums, there was an average decrease in platelet count of only 2 per cent after forty-five minutes and 3 per cent at the end of ninety minutes. The morphologic appearance of the cells was unchanged during the test period. Serums of patients with symptomatic (nonthrombopenic) purpura similarly failed to cause significant platelet agglutination or lysis during a test period of ninety minutes (Table 2).

In contrast, 50 per cent of patients with idiopathic thrombopenic purpura gave a positive test for the presence of circulating antiplatelet antibody. There was an average decrease in platelet count of 17 per cent at forty-five minutes and 24 per cent after ninety minutes (Table 3). When follow-up tests were made on the same patient, at a later date, no apparent change in antibody status resulted from cortisone therapy or improvement in clinical status (Table 4). Morphologic changes, when present, approximated the degradative alterations seen in old platelets after prolonged storage: chiefly blebbing and ballooning. These changes were not consistent, however, and could not, by themselves, be used to differentiate the positive from the negative serums.

Whereas half the patients with idiopathic thrombopenic purpura gave strongly positive evidence of circulating antiplatelet factors, 25 out of 26 consecutive tests on patients with secondary thrombopenic purpura gave negative results (Table 5). The average decrease in platelet count in these 25 tests was 2 per cent at forty-five minutes and 3 per cent at ninety minutes, or the same as that of normal control serums. The cases tested included thrombopenic states secondary to radiation, neoplastic disease and various types of bone-marrow depression (Table 6). The single positive test in the group of secondary purpuras occurred in a case of multiple myeloma that was characterized by marked thrombopenia with fulminating hemorrhages after three months of illness. The possibility of a coincident idiopathic thrombopenic purpura in this patient was suggested by the clinical data.

Nine serums were tested from 7 cases of "hypersplenism." The criteria for the diagnosis of hypersplenism were chronic hepatosplenomegaly in the

TABLE 8. *Platelet Counts and Antibody Tests in Hypersplenism.*

Patient	Fall in Count at 45 min.	Fall in Count at 90 min.	Test for Circulating Antibody	Remarks
	%	%		
B. R. L.	2	16	Positive	Chronic splenomegaly for 8 yr.
— B.	5	5	Negative	Splenomegaly & pancytopenia
M. C.	4	16	Positive	Hepatosplenomegaly & pancytopenia; normoblastic bone marrow.
W. G.	5	19	Positive	Chronic splenomegaly for 18 yr.
W. G.	3	10	Positive	Same case 1 wk. after splenectomy
W. G.	1	6	Negative	Same case 6 wk. after splenectomy & total gastrectomy
G. (L. K. D.)	2	15	Positive	Chronic thrombopenia & splenomegaly for 4 yr.
L. B.	3	5	Negative	Cirrhosis, splenomegaly & purpura
R. A. S.	5	16	Positive	Chronic splenomegaly

TABLE 9. *Fall in Platelet Count in Acquired Hemolytic Anemia.*

No. of Cases	Range at 45 min.	Range at 90 min.	Average at 45 min.	Average at 90 min.
	%	%	%	%
Negative 5	1–4	2–6	3	4
Positive 2*	6–11	12–13	9	13

*All patients in this group had received repeated transfusions.

TABLE 10. *Platelet Counts and Antibody Tests in Hemolytic Anemia.*

Patient	Fall in Count at 45 min.	Fall in Count at 90 min.	Test for Circulating Antibody	Type of Hemolytic Anemia
	%	%		
G. S.	6	12	Positive	Acquired*
M. S.	1	2	Negative	Acquired hemolytic anemia
N. W.	4	5	Negative	Secondary to leukemia
J. A. L.	3	6	Negative	Acquired
M. Z.	11	13	Positive	Acquired
N. A. H.	1	1	Negative	Acquired
R. H. P.	4	5	Negative	Acquired

*Patient had received repeated transfusions over a period of many years.

presence of normoplastic or hyperplastic bone marrow containing adequate numbers of megakaryocytes. There were 6 positive and 3 negative tests (Table 7). The positive tests in this group showed no significant decrease in platelet count at forty-five minutes and an average fall of 15 per cent at ninety minutes. This was in contrast to the positive cases of idiopathic thrombopenic purpura, which showed a 15 per cent fall within forty-five minutes and had almost twice as great a fall after ninety minutes. Included among the positive tests was a single case (Table 8) in which the serum became negative six weeks after splenectomy and total gastrectomy for purpura and bleeding esophageal varices.

Hemolytic anemia was the only disease in which false-positive tests were observed (Table 9). In 7 cases of hemolytic anemia the tests were negative in 5 and positive in 2. One of these 2 positive tests occurred in a patient who had been repeatedly transfused over a period of many years (Table 10), suggesting the possibility of immune platelet isoantibody formation as noted by Harrington.[13]

Discussion

The data derived from the use of this test for the demonstration of antiplatelet antibodies in vitro have several implications. In the first place, a significant number of cases of idiopathic thrombopenic purpura are due to the presence of circulating antiplatelet factors. Although the incidence of positive tests among the cases of idiopathic thrombopenic purpura in this series was approximately 50 per cent, determination of the frequency of humorally induced idiopathic thrombopenic purpura must await more extensive use of this and other types of screening tests.

Platelet antibodies are rarely if ever found in the serum of patients with secondary thrombopenic purpura. As such, the test can aid in the differentiation of these two clinical entities. Although a negative test does not militate against the possibility of primary idiopathic thrombopenic purpura, a positive test is strong evidence against the presence of secondary thrombopenic purpura.

The thrombopenia associated with chronic splenomegaly and cellular bone marrow (hypersplenism) may not always be due to a single factor. In 6 of 9 tests, a positive antiplatelet factor was demonstrable. In 3 of 9 tests, no platelet antibody was found. The positive serum in this group differed from that in idiopathic thrombopenic purpura by a slower action and lessened degree of platelet destruction.

Summary

An in vitro test for use in the classification of antibody-induced thrombopenic purpura is described and discussed. It is suggested that such a classification can aid in the selection of therapy, particularly in the decision of which patients can benefit from platelet transfusions. The use of the test in the differentiation of primary and secondary purpura is discussed.

I am indebted to Drs. Louis K. Diamond, Wayne Rundles and William Harrington for many of the serums used in these tests.

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AMEBIC HEPATITIS PRESENTING AS FEVER OF UNKNOWN ORIGIN*

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THE protean nature of amebiasis has been amply discussed,[1-7] and because of increased alertness to the various clinical syndromes that it may produce, the frequency of its diagnosis has increased during the past ten years.[8-10] Thorough analyses by Klatskin,[3] DeBakey and Ochsner,[4] Sodeman[5, 6] and others have clearly outlined the clinical features of amebic dysentery, hepatitis, involvement of other organs and the "asymptomatic carrier state." Amebic hepatitis, however, presenting as obscure fever has been insufficiently described. In uncomplicated intestinal amebiasis, fever is relatively rare; Browne and his co-workers[11] cited the presence of low-grade fever in only 6.5 per cent of 790 cases of uncomplicated amebiasis.

DeBakey and Ochsner[4] analyzed 263 cases of amebiasis. They found that fever was present in 87 per cent, "liver pain" and tenderness in 89 per cent and hepatomegaly in 77 per cent of 36 patients with hepatic involvement. Only 27 per cent had concomitant diarrhea; an additional 39 per cent had a history of diarrhea. It is evident from their work and from that of others[2-6] that the combination of fever with hepatomegaly, right-upper-quadrant pain and tenderness, and a history of diarrhea should lead to the correct diagnosis of amebic hepatitis.

There have been few observations, however, stressing the fever and prostration that may be present in amebiasis for a long period without diagnostically helpful accompanying symptoms and signs. Patients with this clinical picture may present as "fever of unknown origin." Klatskin, in his study of amebiasis among military personnel in India, cites examples of fever preceding the onset of "liver pain" and tenderness. He states that such patients were at times "thought to have one of the infectious diseases on admission to the hospital." One patient in the series of Sodeman and Lewis[5] had no localizing signs, and this case was diagnosed as "fever of unknown origin."

Similarly, in amebic granuloma of the cecum, obscure fever may be the only presenting feature. Two cases with prolonged histories of fever and weakness, eventually diagnosed as cecal amebiasis, were described by Golden.[12, 13] The recent literature dealing with the subject of cryptogenic fever[14-17] mentions amebiasis only casually, with emphasis on the diagnostic importance of concomitant hepatic tenderness and hepatomegaly. The 2 cases described below are of interest as examples of amebic hepatitis presenting as obscure fever.

TABLE 1. *Laboratory Data in Case 1.*

DATE	HEMOGLOBIN	HEMATOCRIT	WHITE-CELL COUNT	NEUTROPHILS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	SEDIMENTATION RATE	URINARY SEDIMENT	ALBUMIN	GLOBULIN
	gm./100 cc.	%	x10³	%	%	%	%	mm./hr.		gm./100 cc.	gm./100 cc.
Before treatment:											
2-5	11.7	37	12.6	77	11	9	2	36	Abnormal*	3.7	3.2
2-10	10.1	35	17.4	75	21	2	2	33	Abnormal*	3.8	4.0
3-11	9.4	33	6.2	60	37	3	0	26	Abnormal*	2.6	3.95
After treatment:											
4-14	13.1	44	8.4	56	38	3	3	11		3.5	2.85
6-6	—	—	—	—	—	—	—	—	Normal	—	—
3-11	13.6	47	8.25	54	42	3	1	10	Normal	—	—

*A varying number of hyaline and granular casts, oval fat bodies and occasional red cells were seen in the urinary sediment. One specimen showed an occasional red-cell cast. No Addis counts were done. After treatment the urinary sediment was normal.

CASE REPORTS

CASE 1. G. H., a 34-year-old bulldozer operator, was admitted to the hospital on February 5, 1952, with a history of malaise, anorexia, weight loss and low-grade fever of 6 weeks' duration. At the onset of symptoms there had also been cough and a slight pain in the right lower aspect of the chest that had disappeared after 3 or 4 days. There had been no diarrhea during the immediate or remote past. The past history was otherwise noncontributory.

Physical examination showed a man who seemed acutely ill and was perspiring freely but did not complain of pain. The abnormalities were confined to minimal enlargement of the liver, the edge of which extended to 1 cm. below the right costal margin, with slight tenderness on deep palpation. There were several small subcutaneous lipomas on the arms and trunk. The spleen did not appear to be enlarged.

The temperature was 101°F., and the pulse 72. The blood pressure was 120/75.

The laboratory findings are presented in Table 1.

Because of the lack of any localizing signs, initial management consisted of supportive treatment and diagnostic procedures for

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the elucidation of the cause of the febrile illness. Serial chest roentgenograms, blood and bone-marrow cultures and hematologic analysis, pyelography and roentgenographic examination of the upper gastrointestinal tract and the gall bladder disclosed no abnormalities. The results of the agglutination tests for typhoid, paratyphoid, brucellosis and *Proteus X19* were also within normal limits. The tuberculin skin test was negative. Occult blood (+ to ++ guaiac tests) was consistently found in the feces. Stool cultures failed to reveal any pathogenic organisms. Initial examination of purged stools performed on 2 successive days also failed to demonstrate *Endamoeba histolytica* or other parasites. The tests of hepatic function showed slight abnormality (Table 1). A specimen of liver obtained by needle biopsy via the intercostal route revealed only focal necrosis, but was of no specific diagnostic assistance (Fig. 1). Biopsy specimens of the subcutaneous nodules taken from 3 different sites disclosed histologic features typical of lipoma. At this time, because of the abnormal urinary sediment (Table 1) the possibility of visceral angiitis was considered. A test for the L. E. (lupus-erythematosus) plasma factor was negative.

One month after admission, barium-enema examination showed narrowing of the cecum, with slight dilatation of the terminal ilium. This observation was the first helpful clue to the diagnosis of amebiasis as the cause of the fever. Again, the examination of purged stools was undertaken, and on this occasion, 2 of the 4 stools examined revealed trophozoites of *E. histolytica*. Five weeks after admission treatment with emetine, 60 mg. daily, intramuscularly, was started. Thirty-six hours after the initial dose the temperature returned to normal, and the patient noted marked subjective improvement. On the 6th day of treatment an electrocardiogram revealed flattening of the T waves and prolongation of the QT interval. Emetine treatment was therefore discontinued, and treatment with chloroquine was initiated. This was given in a dosage of 1 gm. daily for 2 days followed by 0.5 gm. daily for 20 days, all by the oral route. Diiodoquin in a dosage of 2 gm. daily was given concurrently with the chloroquine. The response to treatment was dramatic, with rapid recovery.

The patient has subsequently been seen at frequent intervals and has been completely well. The deformity of the cecum noted in the initial roentgenographic examination has persisted, however.

Repeated examination of the purged stools after clinical recovery failed to reveal *E. histolytica*. The complement-fixation test, which had been positive (Table 1), when retested showed a marked decrease in the titer.

Table 1 (*Concluded*).

Date	Cephalin Flocculation	Thymol Turbidity units	Bromsulfalein Retention %	Bilirubin direct mg./100 cc.	Bilirubin total mg./100 cc.	Nonprotein Nitrogen mg./100 cc.	Amebic Complement Fixation
Before treatment:							
2-5	+++	1.2	4.5	—	—	—	—
2-10	Negative	0.9	—	—	—	37	—
3-11	—	—	6.0	0.15	0.9	—	++++ (1:128)
After treatment:							
4-14	Negative	1.2	—	—	—	—	—
6-6	—	—	—	—	—	—	++ (undiluted)
3-11	—	—	3.0	—	—	—	—

Case 2. D. C., a 25-year-old railroad worker was admitted to the hospital on January 27, 1952, complaining of lightheadedness and several fainting spells for 4 days before admission. He stated that his physician had found a "slightly elevated" blood pressure. He admitted to the consumption of 6 to 8 glasses of beer daily during the past year. During the past year he had had an occasional watery stool, which, however, had caused him no inconvenience or distress.

There was a family history of hypertension. In infancy he had had an operation for pyloric hypertrophy.

Physical examination showed an obese man (weight 233 pounds) with a withdrawn, apathetic personality. The heart was not enlarged, and the heart sounds were normal. Because of the obesity and poor co-operation, palpation of the abdomen was considered unsatisfactory. There was, however, no tenderness, and neither the liver nor the spleen was enlarged to palpation.

The temperature was 100°F., and the pulse 110. The blood pressure was 156/110.

The laboratory findings are presented in Table 2.

Shortly after admission the blood pressure returned to normal levels. Because of the low-grade fever, the history of alcoholic intake and the initial hyperbilirubinemia, the possibility of cirrhosis of the liver was considered. The tests of hepatic function (Table 2), however, were only slightly abnormal, and returned to normal within a few days of admission. A specimen of the liver obtained by needle biopsy revealed minimal fatty metamorphosis and scattered areas of focal necrosis (Fig. 2). These changes were considered insufficient to warrant the diagnosis of cirrhosis or other intrinsic hepatic disease as a cause of the hyperbilirubinemia or fever. Roentgenographic examination of the entire gastrointestinal tract and the gall bladder revealed no abnormalities. The skin reaction to 0.005 mg. of PPD (purified protein derivative) was weakly positive. Electrocardiograms initially were considered normal. The low-grade fever persisted, with no apparent clue to the cause until 4 weeks after admission. On that day and for the next 2 days the temperature rose to 102°F., subsequently returning to its previous low-grade level. At this time equivocal right-upper-quadrant tenderness was noted. A roentgenogram of the chest taken on the following day demonstrated elevation of the right leaf of the diaphragm, with areas of focal atelectasis in the right lower-lung field (Fig. 3*A*). This represented a distinct change from the roentgenogram taken shortly after entry to the hospital (Fig. 3*B*). Bronchoscopic examination at this time was negative. The appearance of the elevated diaphragm led to fruitless numerous examinations of purged stools for *E. histolytica*.

Three weeks later a strongly positive complement-fixation test for amebiasis was obtained. A presumptive diagnosis of amebic hepatitis was made. Emetine was then administered in a dosage of 60 mg. daily intramuscularly for 10 days, followed by a course of chloroquine and diiodoquin in the usual dosage administered concurrently. The temperature did not return to normal until 10 days after the initiation of emetine therapy but remained normal thereafter. During this period the abdominal tenderness also disappeared. The electrocardiogram after the course of emetine showed nonspecific T wave changes consistent with an emetine effect. Throughout his hospital course the patient showed a schizoid personality. One month after completion of treatment of the amebiasis he was transferred to the psychiatric service.

Discussion

Zavala and Hamilton[18] recently enumerated the following helpful clues to the differential diagnosis of amebic hepatitis: "(1) tender and often enlarged liver; (2) fading suntan complexion of the skin; (3) elevation and fixation of the right leaf of the diaphragm; (4) little or no change in liver function tests; (5) positive complement fixation test with a

fall in titer following specific amebicidal therapy; and (6) specific therapeutic response to amebicidal drugs."

Attention is called to the late appearance of such classic signs of amebic hepatitis as a tender, enlarged liver in both cases reported above and elevation and fixation of the right leaf of the diaphragm in Case 2. The "fading suntan complexion of the skin" was not noted in either patient. Of interest was the bradycardia in Case 1 since Klatskin[3] has emphasized the fact that the relative bradycardia in febrile patients with amebic hepatitis resembles that encountered in typhoid fever.

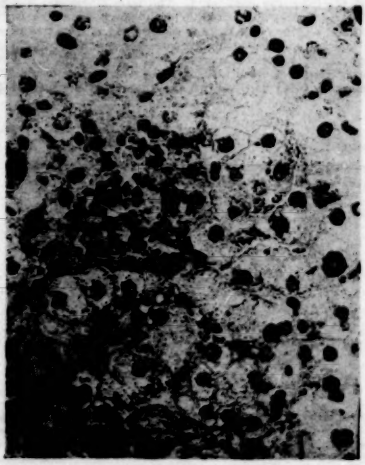


FIGURE 1. *Liver-Biopsy Section in Case 1, Showing Focal Necrosis.*

The tardiness of diagnosis in these 2 cases and in a number of those described in the literature seems to have been related to the delay in the development of clinical features assumed to be classic for hepatic amebiasis. The hepatic tenderness and enlargement and the elevation and fixation of the diaphragm may not appear soon enough to be of much diagnostic aid.

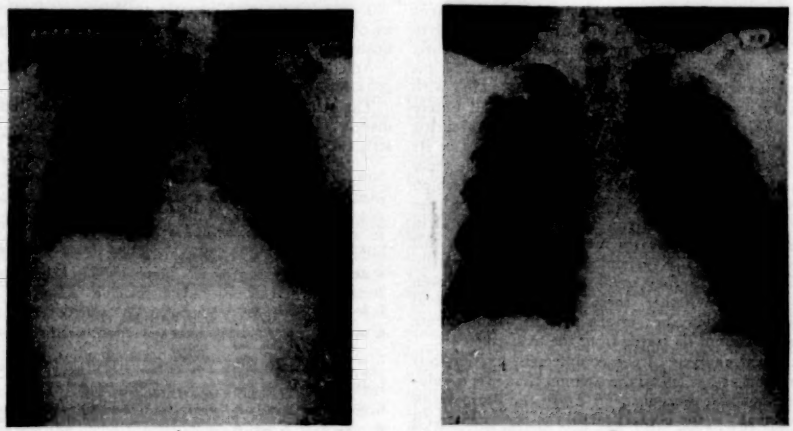
FIGURE 2. *Liver-Biopsy Sections in Case 2, Showing Focal Necrosis.*

Contrary to what may be expected in a presumably diffuse hepatitis, liver-function and biopsy studies are of little specific significance in amebic hepatitis. Brown and Hodgson[19] described abnormal bromsulfalein retention in hepatic amebiasis. Klatskin[3] observed bile in the urine of patients with acute and subacute amebic hepatitis. Sodeman and Lewis[5] stated that amebic disease of the liver is largely "an insular type of involvement" and, therefore, infrequently productive of abnormal hepatic function. They referred to "an occasional" case showing a positive cephalin-flocculation or

TABLE 2. *Laboratory Data in Case 2.*

DATE	HEMOGLOBIN	HEMATOCRIT	WHITE-CELL COUNT	NEUTROPHILS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	SEDIMENTATION RATE	URINARY SEDIMENT	ALBUMIN	GLOBULIN
	gm./100 cc.	%	x10³	%	%	%	%	mm./hr.		gm./100 cc.	gm./100 cc.
Before treatment:											
1–28	18.6	57	11.0	61	32	6	1	2	Normal	4.17	2.18
2–4	14.4	51	7.0	60	31	8	1	5	Normal	—	—
2–29	—	46	12.75	78	10	10	2	30	Normal	4.65	2.35
3–17	—	47	7.4	68	30	2	0	4	Normal	—	—
After treatment:											
5–13	12.9	46	6.55	54	40	4	2	7	Normal	3.89	2.6

thymol-turbidity test, and emphasized the infrequency of chemical or clinical jaundice. Similarly, Klatskin found elevation of the icteric index in only 1 of 13 patients studied. Bonnin and Moretti[20] an abnormal value of the cephalin flocculation test was found. In both patients the tests of hepatic function yielded normal results after treatment. It is of interest that, although the specimens of liver



A B

FIGURE 3. *Roentgenograms of the Chest in Case 2 Taken on Entry* (B) *and One Month Later*. (A).

recently reported a study of hepatic function and structure in 4 cases of amebic colitis. They describe abnormal values for the thymol-turbidity and cephalin-flocculation tests in all cases. Liver biopsy in these patients showed varying degrees of portal fibrosis and areas of focal inflammation. The authors suggest that, in addition to the cases of frank amebic hepatitis, hepatic involvement due obtained by needle biopsy in both patients failed to reveal amebas, both showed focal necrosis such as that described in experimental and clinical amebic hepatitis.[20-23] These observations support the opinion of Zavala and Hamilton[18] that normal hepatic function should not be construed as excluding the diagnosis of hepatic amebiasis. On the contrary, it is the usual laboratory feature of that disease.

TABLE 2 (*Concluded*).

DATE	CEPHALIN FLOCCULATION	THYMOL TURBIDITY	BROMSULFALEIN RETENTION	BILIRUBIN		ALKALINE PHOSPHATASE	NONPROTEIN NITROGEN	AMEBIC COMPLEMENT FIXATION
				DIRECT	TOTAL			
		units	%	mg./100 cc.	mg./100 cc.	units/100 cc.	mg./100 cc.	
Before treatment:								
1-28	—	2.6	—	1.5	2.4	2.4	44	—
2-4	++	—	7.0	0.1	0.8	—	47	—
2-29	+	—	—	0.65	1.05	2.45	51	—
3-17	—	—	—	0.45	0.75	—	—	++++
After treatment:								
5-13	Negative	2.2	5.5	0.1	0.25	2.2	29	++++

to amebic invasion is common in patients considered to have only amebic colitis. One of the patients described above had minimal elevation of the serum bilirubin level. In both cases there was slight abnormality of bromsulfalein retention, and in 1 of the 2 an elevated serum globulin level with

The abnormalities of the urinary sediment in Case 1 are of interest. Blood casts and oval fat bodies were found on repeated examinations of the urine during the acute phase of the illness. The finding of blood casts in the urine represents a glomerulitis.[24] Oval fat bodies are presumably

desquamated, degenerated, fat-laden, tubular epithelial cells.[24] The disappearance of these abnormalities as the patient recovered support their relation to the amebiasis. Urinary amebiasis has been discredited by most observers.[25] It has been stated that only when an amebic abscess ruptures into the urogenital tract does actual amebic involvement occur. The significance of the parenchymal involvement of the kidney in amebic hepatitis is obscure. It is of interest, however, that Rappaport and his co-workers,[26] in describing arthritis associated with intestinal amebiasis, stated that "although purely speculative our suggestion is that amebic arthritis is the result of sensitization to E. histolytica or its by-products." If this suggestion is valid, the renal changes observed in Case 1 might well have been on this basis. Further observations of abnormalities of the urinary sediment in amebic hepatitis and in other extrarenal diseases may throw light on this problem. In many systemic diseases, not primarily involving the kidney, oval fat bodies have been observed.[27] Whether these present "the larval nephrosis"[28] described in the past in various acute diseases cannot be stated from the available data.

Critical analysis of the complement-fixation test in amebiasis has led to the opinion that it is a valuable diagnostic procedure.[29-31] Terry and Bozicevich[29] state that "if the clinical picture is consistent with amebic hepatitis or liver abscess, the complement fixation test is far more reliable than a history of diarrhea, stool findings, or proctoscopic examination." Although the specific significance of positive complement fixation for amebiasis remains to be established, a strongly positive result in a patient with a compatible clinical picture is considered highly suggestive of extraintestinal involvement by most observers. A fall in titer with treatment is accepted as strongly corroborative evidence. The complement-fixation test was strongly positive before treatment in both cases reported above. In Case 1 there was a marked fall in the titer after treatment. In Case 2 no decrease in the titer of complement-fixing antibodies could be demonstrated during the period of observation, but this patient did not return for further studies. Although in the cases described the complement-fixation test served only to support the clinical diagnosis, it is believed that the earlier use of this test might have led to the correct diagnosis with less delay.

The difficulty in arriving at the diagnosis in the 2 cases presented should not be construed as support for a therapeutic test with amebicidal drugs in cases of obscure fever. The known toxicity of emetine and the nonspecificity of chloroquine preclude such an approach to the management of obscure fever. The recognition, however, that fever of unknown origin may be due to amebic hepatitis will lead to the appropriate diagnostic studies and their careful evaluation. Nevertheless, the failure to find *E. histolytica* in the feces as illustrated by the cases described above does not exclude early amebic hepatitis.

Summary and Conclusions

Two patients with hepatic amebiasis presenting as obscure fever are described. In both the diagnosis was established only after long delay.

Amebiasis should be included in the diagnostic consideration of fever of obscure origin.

The clinical and laboratory features of this disease are reviewed, with special emphasis on structural and functional changes of the liver.

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CRYOGLOBULINS IN CORONARY-ARTERY DISEASE*

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COMPREHENSIVE essays on cold-precipitable substances in serum have been provided by Barr, Reader and Wheeler,[1] and by Lerner and Watson,[2] who suggested the descriptive term "cryoglobulin." Such substances probably include several groups of proteins, and perhaps other compounds. When present in large amounts, cryoglobulin of itself produces a well defined clinical syndrome similar to Raynaud's disease. Although Rörvik[3] stated that even small amounts of cryoglobulin must be considered pathologic, only one clinical study of a disease with small amounts of cold-precipitable substance has been made. That report, by Dreyfuss and Librach,[4] suggested that the high incidence of cold-precipitable substance in subacute bacterial endocarditis might be employed as a diagnostic adjunct.

Since large amounts of cryoglobulin often cause the blood to gel at commonly encountered temperatures, one might speculate that small amounts could increase the blood viscosity to a lesser degree. Such a situation would be hazardous in patients with vessels predisposed to thrombosis by arteriosclerotic narrowing. The cold sensitivity of patients with coronary-artery disease initiated our speculation that their cold intolerance might be related to the physical alteration of certain blood proteins.

Redisch, Sheckman and Steele[5] recently described the usual temperature of the toes in a room at 20°C. as being about 21°C. This is a level at which high concentrations of cryoglobulin not only thicken but gel. Since it has been demonstrated that gelled cryoglobulinemic serum requires prolonged warming to regain normal fluidity,[3] blood thickened by exposure in the extremities probably remains more viscous than normal throughout the circulation. Multiple thromboses due to cryoglobulinemia have been suggested as a cause of pulmonary fibrosis.[6]

Our attempt to correlate coronary-artery disease and cryoglobulinemia was further stimulated by two other studies. Wilson and Finch[7] demonstrated changes in the electrocardiogram produced by drinking of ice water. Raynaud[8] described characteristic alteration of serum globulin during myocardial infarction.

METHODS

Unfortunately, in the majority of patients with cold-precipitable serum substances the small amounts present are insufficient for even the most elementary chemical studies. From the behavior of the serum of patients with large amounts of cryoglobulin, deductions have been made regarding the identity of trace quantities. In severe cryoglobulinemia the serum gels or precipitates on cooling. From this observation it has been assumed that minute precipitates induced by refrigeration are also cryoglobulins.

For the detection of trace cryoglobulinemia the procedure employed[1, 2] is as follows. Blood is obtained from fasting patients and kept at 37°C. until it clots. The serum is separated and refrigerated at 4°C. Observations are made each twenty-four hours for a week, most positive tests appearing by the third day. A positive test consists in the appearance of a white opacity (fine precipitate or flocculation) at 4°C., which redissolves at 37°C. We used two tubes of serum and compared the warmed tube to a cold one. A positive test was graded in the following manner: + signified definite but fine opalescence in the cold test tube with clear serum in the warm tube, and ++ gross precipitate or flocculation in the cold test tube. We encountered no serums that gelled on cooling.

Attempts to separate the precipitate for analysis were unsuccessful. The substance must be repeatedly washed to remove contaminating normal serum protein, and is usually lost during washing.

Two common causes of false-positive tests are the delayed coagulation of fibrinogen and lipemia. Fibrinogen can be differentiated from cryoglobulin because it does not redissolve on warming. Lipemia is more difficult to differentiate, but can be avoided if blood is obtained with the subject fasting.

Our study was undertaken to determine the incidence of cryoglobulinemia in patients with coronary-artery disease and to observe whether there was any correlation with the clinical course. Sixty-nine patients were studied. Four had severe angina pectoris without myocardial infarction, and 65 had had a recent infarction proved electrocardiographically. Single tests for cryoglobulins were performed on 35, and two or more serial tests on 34 patients; serial tests were done at weekly intervals.

Corollary studies of cold agglutinins, dilution turbidity tests and blood cholesterol determinations were made in some patients. The dilution turbidity test[9] is a crude index of the amount of cryoglobulin present, and may be interpreted similarly to the thymol turbidity test (results of 1 to 4 units are normal).

Viscometry was performed on 16 serums, 9 of which gave positive tests for cryoglobulins. Ostwald

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viscometers immersed in a constant-temperature water bath were used for these determinations, which were made at both 5 and 37°C.

Results

The tests for cryoglobulins are summarized in Table 1. Serial examinations increased the likelihood of obtaining a positive test, and only 13 of 34 patients had no positive test on repeated examination. In 13 other patients, who had both positive and negative tests on successive observations, the early tests were more often negative. Eight patients who had repeatedly positive tests showed no increase in positivity — that is, reactions of + to ++.

Table 1. *Tests for Cryoglobulin.*

Type of Test	Result	No. of Tests
Single:		
	++	3
	+	4
	0	28
Total		35
Serial:		
	++	19
	+	28
	0	52
Total		99

Positive tests did not correlate with high titers of cold agglutinins, positive dilution-turbidity tests or hypercholesterolemia. Four negative tests were associated with cold-agglutinin titers of 0 to 1:32, and 5 positive tests with titers of 0 to 1:16. Twenty-three patients with negative tests had dilution turbidity tests of 0 to 4 units (a normal range); 5 with positive tests had turbidities of 0 to 4 units. Ten negative tests were associated with blood cholesterol levels of 124 to 281 mg. per 100 cc., and 10 positive tests with levels of 149 to 278 mg. per 100 cc.

Addition of heparin solution or Dicumarol to a serum containing cold-precipitable substances did not alter the turbidity.

Viscosity of serum from 7 patients with negative tests and 9 patients with positive tests was measured at 5°C. and at 37°C. (Table 2). The viscosity of serum from both groups of patients was normal at both temperatures, and was unaffected by the presence of cryoglobulin.

Table 2. *Average Relative Serum Viscosity.*

Cryoglobulin Test	At 5°C.	At 37°C.
Positive (9 patients)	1.65	1.46
Negative (7 patients)	1.65	1.45

The 65 patients with myocardial infarction all had periodic complete blood counts and erythrocytic sedimentation rates, and the majority exhibited the typical early elevation of the neutrophil percentage, total white-cell count and erythrocytic sedimentation rate. There was no correlation between these changes and the incidence of cryoglobulinemia, nor between the typical early low-grade fever and cryoglobulinemia.

Discussion

Large amounts of cryoglobulin have been found in multiple myeloma, kala-azar, lymphosarcoma and polyarteritis nodosa.[10-13] Small amounts have been detected in a large number of apparently unrelated diseases.[1, 2] The only correlation between cryoglobulinemia and any other test is that it seems to occur more commonly in diseases with disturbance of the blood proteins. Our findings confirm previous reports of the independence of cryoglobulinemia and changes in cold agglutinins, euglobulin, blood cholesterol and sedimentation rate.

It is probable that a large number of substances are cold precipitable from the serum, and that the same substance present in the same concentration may precipitate or gel in the serum of one person and not in another. Wintrobe and Buell,[14] who were the first to describe a cold-precipitable serum protein, warned against accepting such physical properties as reliable characteristics, since so many factors (electrolyte concentration, blood pH, oxygen or carbon dioxide concentration, transported enzymes and so forth) could influence phenomena like gelation and precipitation.

Immunochemical methods have been suggested as an approach to recognition of trace amounts of abnormal serum proteins.[15] Since an unknown number of different substances are cold precipitable, an acceptable test would have to embrace so many different immunologic possibilities that its nonspecificity would limit its usefulness.

In view of our normal viscometric results, it seems injudicious to attach significance to the presence of small amounts of cold-precipitable substances in the serum of patients with coronary-artery disease, at least until such substances are better defined.

Summary and Conclusions

Cold-precipitable substances in small amounts were present in the serum of 40.6 per cent of 69 patients with coronary-artery disease.

Seven serums with negative tests and 9 with positive tests exhibited normal viscosity at both 5°C. and 37°C.

In view of the normal viscosity, the significance of these small amounts of cold-precipitable substances can only be speculated on.

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MEDICAL PROGRESS

DEVELOPMENT OF KNOWLEDGE CONCERNING THE GASTRIC INTRINSIC FACTOR AND ITS RELATION TO PERNICIOUS ANEMIA*

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THOMAS ADDISON,[1] physician to Guy's Hospital, London, published his classic description of pernicious anemia in 1855. Since then nature has held almost a ninety-nine-year lease on a recognized mystery. Happily, her foreclosure of the mortgages on the lives of the tenants of this disorder has become rare since 1926. At that time George R. Minot and William P. Murphy, of Boston, discovered what was in effect a regular means of cure for pernicious anemia. Although their liver feeding and its subsequent refinements by others saved many lives, the exact cause of the disease has remained obscure. Today, however, it can be stated with assurance that pernicious anemia is usually an example of a highly specific isolation of the affected person from his alimentary environment. Thus, this disease would not develop if the patient could effect daily the transfer of a millionth of a gram of vitamin B_{12} the distance of a small fraction of a millimeter across the intestinal mucosa and into the blood stream. This he cannot do, principally as a result of failure of his stomach to secrete into its lumen some essential but still unknown substance. Yet the patient may each day absorb without much difficulty the products of the digestion of many grams of carbohydrate, fat or protein from foods that in addition may contain consequential amounts of vitamin B_{12} in terms of his trivial need. Such starvation in the midst of plenty has elsewhere been called "conditioned deficiency disease."[2]

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GENERAL NATURE OF PERNICIOUS ANEMIA

Until very recently the nutritional defect in pernicious anemia appeared to be peculiar to man. It is now known that vitamin B_{12} is generally essential to animal nutrition.[3-6] However, unlike other accessory food factors, it can be synthesized only by certain bacteria and algae and not by the higher plants. In herbivorous animals, when cobalt is present in the forage, the bacterial production of vitamin B_{12} (cyanocobalamin and related compounds) in the rumen is large. It is thereafter absorbed from the small intestine. In nonruminant animals vitamin B_{12} is probably derived largely from animal food and to an uncertain extent only from synthesis by bacteria in cecum or colon unless coprophagy occurs. In man vitamin B_{12} deficiency causes among other biochemical disturbances defective synthesis of nucleoprotein.[4-6] Translated into microscopically visible effects in pernicious anemia this means that without unimaginably small traces of vitamin B_{12} many of the body cells are unable to divide to form new cells at the usual rate. Consequently, they grow large. This is most apparent where the production of new cells is normally rapid — for example, in the bone marrow and in the intestinal tract. The characteristic macrocytic anemia of pernicious anemia with few young erythrocytes, the leukopenia and "giant" granulocytes, and the thrombocytopenia reflect the lowered rates of cell division by the bone marrow. The smooth tongue of pernicious anemia is probably also the result of too leisurely a division of its epithelial cells. Graham and Rheault[7] have shown that large epithelial cells are found in the gastric washings and vaginal scrapings of patients with pernicious anemia, and they

become normal in size after therapy with vitamin B_{12}. Interpretation of subacute combined degeneration of the spinal cord, perhaps the most characteristic expression of severe vitamin B_{12} deprivation, has recently been offered in terms of defective ribose nucleic acid synthesis affecting especially the long axones of nerve cells in the spinal cord.[9] Regarding the immediate mechanisms causing the anemia, the conflict between the champions of the "maturation arrest" and the "hemolytic" theories is now happily over. It has been conclusively shown that both views were partly correct though perhaps to a reciprocal degree in a given patient at a given stage of his disease. Thus, the red cells are more slowly produced by the bone marrow[9] and are thereafter apparently more rapidly destroyed than normally.[10] However, as originally suspected by Whipple,[11] 50 per cent of the excess fecal pigment output is not derived from circulating red-cell hemoglobin.[12]

Atrophy of the Stomach

From the description in 1824 of his patient by Dr. Combe,[13] of Edinburgh, it is of course not certain that this was a case of pernicious anemia. More probably, the condition described was aplastic anemia or perhaps the anemia of chronic uremia ("albuginea of the eye bluish . . . tongue covered with a dry fur. . .constant thirst. . .at autopsy muscular substance throughout the body was like that of the heart, very pale. . .pale yellow fat"). However, Combe's speculation about the basis of his patient's anemia perfectly defines the subject of these present remarks: . . ."it is probably owing to some disorder of the digestive and assimilative organs that its characteristic symptom has its origin, and to the correction of this derangement we must look for a removal of the disease." In 1860, five years after the publication of Addison's monograph, Austin Flint,[14] in a lecture to the students of the Long Island College of Medicine at Brooklyn, New York, confidently narrowed the indictment:

> I suspect that in these cases there exists degenerative disease of the glandular tubuli of the stomach. . . .Fatal anaemia must follow an amount of degenerative disease reducing the amount of gastric juice so far that assimilation of food is rendered wholly inadequate to the wants of the body. I shall be ready to claim the merit of this idea when the difficult and laborious researches of someone have shown it to be correct.

It was Dr. Samuel Fenwick, of the London Hospital, however, who first made these guesses historically interesting. In 1870 he[15] established both the histologic cause and a biochemical consequence of the lack of gastric secretion by his post-mortem studies of the stomach in a case that he assumed to be one of Addison's "idiopathic anaemia."

He described his observations as follows:

> When placed beneath the microscope. . .the whole of the glandular structure was in a state of atrophy. . . .I carefully scraped off the mucous membrane from the splenic and middle regions of the stomach and diffused it in two ounces of distilled water along with half a drachm of hydrochloric acid for 12 hours. A cube of hard boiled white of egg, 15 gm. in weight, was then digested for 9 hours at blood heat but at the end of this period the albumin had not lost any weight . . . .The progressive atrophy of the stomach had prevented the digestion of the albuminous materials of the food at the same time that the healthy condition of the liver, pancreas, and intestines admitted a free supply of the other constituents of the body.

How close to the mark this inference was is now appreciated. Indeed, for the years just before its identification as vitamin B_{12} in 1948, the unknown substance was called the "animal protein factor"[16] because of its close association with such "albuminous materials."

Gastric Achlorhydria

Cahn and Mering,[16] in 1886, were the first to demonstrate a lack of hydrochloric acid in the stomach contents of a patient with pernicious anemia during life. By the turn of the century Faber and Bloch[17] had collected 33 cases of pernicious anemia in which the gastric juice had been examined and shown to contain little or no acid. Thirteen of these patients harbored the fish tapeworm. With the introduction of the fractional test meal and the flexible stomach tube of small diameter, studies of larger series of patients excluded other conditions as being without complete achlorhydria and confirmed the constancy of a lack of hydrochloric acid in pernicious anemia.[18, 19] Achlorhydria assumed additional significance by 1925, when Hurst[20] had shown that it was present in 24 patients with subacute combined degeneration of the spinal cord whose anemia he regarded as indistinguishable from that of other pernicious-anemia patients without neural lesions. Moreover, as time passed, achlorhydria was found to have preceded the appearance of pernicious anemia by many years[21, 22] and, like the disease itself, to be distinctly more common in the relatives of persons with established pernicious anemia.[20] Indeed, it occurred in their offspring even as children. The establishment of the constancy of achlorhydria in pernicious anemia owes much to the work of Hurst,[22] who pointed to its persistence during spontaneous remissions of the anemia and to the development of pernicious anemia after gastrectomy as well as occasionally in patients with cancer of the stomach and achlorhydria. Without this emphasis the eventual recognition of the relevance of the specific defect in the gastric secretion might have been further delayed.

The persistence of the English school in seeking a cause for the anemia other than in the "primary" alteration of the bone marrow, first conceived on the continent by Cohnheim and emphasized by Ehrlich, continued to be based on a belief in an external cause of the disorder. It was logical that after Pasteur's work interpretations should be sought

in terms of the increasing number of fruitful discoveries in the field of bacteriology. By 1901 William Hunter[20] had proposed the toxic and hemolytic properties of micro-organisms as an explanation for the hemosiderosis of the liver, and Muir interpreted the hypercellularity of the bone marrow as a response to the anemia so created. Two decades later Hurst [20, 22] regarded the achlorhydria not as secondary to a chronic infective gastritis as Hunter had, but as a primary process leading to a failure of intestinal antisepsis against the *Streptococcus longus*. By the end of the first quarter-century the infectious origin of the disease had been attributed to nearly every organism that inhabits the intestinal canal.[24]

Nutritional Deficiency

During the same twenty-five years, however, an entirely different conception of certain diseases was gaining recognition. This was, of course, the idea that morbid processes may be due not only to positive deleterious influences but also to the negative qualities of defective diets. The concept owes much to Dutch physicians, for it was Eijkman,[25] working in Java, who first produced experimental beriberi in chickens. To his colleague, Grijns,[26] goes the credit for the recognition in 1901 that a dietary deficiency was so operative, not because it failed as an antidote to a hypothetical "beriberi germ," but because it "lacked certain substances of importance in the metabolism of the central nervous system." From his own animal experiments Pekelharing also clearly derived this concept, although he gave no details of his unsuccessful efforts to separate such substances from milk. Interest in the subject soon became worldwide, and it received attention in the laboratories of Hopkins, Osborne and Mendel, McCollum and others. In 1911 Funk crystallized, not a substance, but a concept with the word "Vitamine."[27] The classic observations of Whipple and his associates[11, 28] in America, begun about 1920, established once and for all on a quantitative basis the persistent popular notion, but sometimes wavering professional belief, that the properties of food influence blood formation. If Whipple's careful experiments with chronically bled dogs had initially investigated the hematopoietic activity of inorganic iron salts upon hemoglobin production, the results would have been equally convincing. However, he chose to explore the properties of various foods, including liver and meat, and in this way, fortunately, raised at the very outset of his work questions concerning more subtle nutritional influences.

In the clinical area also, at the time of the discovery of the efficacy of liver feeding in pernicious anemia, beriberi as well as pellagra, with its sore mouth and neural changes, and sprue, with its macrocytic anemia and diarrhea, were under investigation as dietary deficiency diseases. The hematologic resemblances between tropical sprue and pernicious anemia, at least in some patients, were well known to Dutch and British physicians who had observed European patients returning from the tropics with well established sprue. Wood,[29] in North Carolina, where at that time malnutrition on an economic basis was not uncommon, reported cases in which the diagnosis of either pernicious anemia or sprue seemed equally apt. According to Manson-Bahr,[30] in the Hospital for Tropical Diseases in London, liver soup had for years been regarded as "almost a specific in sprue." Particularly significant in retrospect are the therapeutic observations of Elders,[31] who, having become familiar with sprue in Sumatra, on his return to Holland found striking resemblances in cases of pernicious anemia. In 1925 he reported the increases in blood values in a patient with pernicious anemia given the same dietary regimen that he had found during the preceding decade to be invariably successful in cases of sprue: underdone meat, 1 kg. or more, 0.5 to 2 liters of raw milk, 15 to 30 cc. of cod-liver oil, and a few oranges or 400 gm. of strawberries daily. Such a diet was no doubt possible only for those who considered it beyond question that they must eat to live. Elders[31] expressed his conviction that "pernicious anaemia is, like sprue, a deficiency disease, and as such should be curable; or at least amenable to improvement by well chosen food." The following year brought the completely convincing demonstration of the truth of this inspired prediction, when Minot and Murphy,[32] using a diet containing "an abundance of food rich in complete proteins and iron — particularly liver — and relatively low in fat," successfully produced remission of the anemia in 45 patients with pernicious anemia.

In 1925 opportunity came to me to participate in studies of this disorder as assistant resident at the Thorndike Memorial Laboratory of the Boston City Hospital. This laboratory, which is operated jointly by the City of Boston and the Harvard Medical School in conjunction with medical teaching services, had recently been opened with great expectations under the directorship of Dr. Francis Peabody. I was attracted by Dr. Peabody's outstanding personal and professional qualities and because of an interest in pernicious anemia largely based on the conviction that there must be a discoverable causal connection between the almost invariable achylia gastrica and the disease. As it turned out, I was in precisely the right place at the right time to benefit from fortunate circumstances. The concept of dietary deficiency disease was in the air. Occasional patients with pernicious anemia, beriberi, pellagra and scurvy entered the medical wards of the hospital. Soon thereafter, the demonstration of the effectiveness of liver feeding[32] strongly indicated that pernicious anemia was in some sense a dietary deficiency disease[33]; the changes thereby induced in the bone marrow sug-

gested to Peabody[24] the concept of maturation arrest of erythropoiesis. These findings also immediately raised the question why most persons were able to stave off the disease without eating half a pound of liver a day as was required of the patients of Minot and Murphy. It appeared likely to me that "by substituting some digestive process of the normal stomach. . .it might be possible to affect the patient's disease favorably."[25] The reticulocyte responses utilized so effectively by Minot and his associates[26] in their early attempts to assay the activity of liver seemed to provide a means of testing this hypothesis within a few days. Being then unaware of the writings of Flint[14] and of Fenwick,[15] I was deprived of the encouragement that would have come from sharing their convictions.

Nutritional Deficiency Conditioned by Achylia Gastrica

In the clinical observations "the effect of the peptic digestion of protein was first undertaken."[25] The procedure most nearly resembling the operations of nature seemed to be the soundest plan. Consequently, the first attempt was to determine whether or not the daily administration by Rehfuss tube of the liquefied stomach contents of a healthy normal person removed an hour after the ingestion of 300 gm. of lean beef muscle would be hematopoietically effective in a patient with untreated pernicious anemia. It was assumed that about 100 gm. of beef muscle would not be recovered from the donor's stomach. Therefore, during a preliminary ten-day control period 200 gm. of beef muscle was administered to the patient daily. This caused no detectable hematopoietic or clinical effect. However, in the immediately succeeding period, when the stomach contents were given daily, a reticulocyte response of moderate degree appeared, the patient improved clinically, and the red cells and hemoglobin began a gradual increase that continued for forty days while this therapy was maintained, quite as if the patient had been receiving moderate amounts of liver by mouth. Naturally, this was most encouraging. In other patients it was soon shown that from 150 to 300 cc. of normal human gastric juice secreted under the stimulus of histamine was without effect when given alone,[27] as was 200 gm. of beef muscle *even after complete digestion with pig pepsin.*[28] However, when beef muscle and gastric juice were given *together* at pH 5 to 7, with or without previous incubation with pepsin and hydrochloric acid for six hours in vitro, the hematopoietic effects resembled those obtained with the original beef-muscle-containing stomach contents. Consequently, it was assumed that some unknown but essential interaction between beef muscle as an extrinsic (food) factor and normal human gastric juice as an intrinsic factor appeared to be required for the restoration of normal hematopoiesis in the patient with pernicious anemia.

During the conduct of these and of all subsequent observations the diet of the patient was arbitrarily restricted so as to contain no meat, fish or eggs, and very little milk. Substances with known hematopoietic activity such as liver, kidneys and pharmaceutical preparations were, of course, excluded. The usual plan of observation involved successive consecutive periods of ten days or more, during each of which the material under test was given in uniform daily amounts. Meanwhile, daily reticulocyte counts and frequent determinations of red cells and hemoglobin were made. Conclusions regarding the hematopoietic activity of the material given during any one period as compared with that given during the immediately preceding period have been largely based on the method of the so-called "double reticulocyte response," the interpretation of which has been carefully defined elsewhere.[29] These experimental principles have been employed with slight modification whenever clinical studies of this type were made in pernicious anemia by my associates and myself during the past twenty-five years. From these men and women, whose names appear with mine in the bibliography, has come the stimulation and renewed curiosity that has directed our studies. Fortunately, the subject has attracted the productive attention of clinical investigators in the United States and in other countries. Time, however, permits the discussion of only some of the many questions and of the fewer present answers that pertain to the nature and functions of the so-called intrinsic factor.

The Food (Extrinsic) Factor

An interaction between beef muscle and gastric juice having thus apparently been established,[27, 28] it was considered of interest to ascertain the nature of the presumed food substrate of the intrinsic factor. Soon it was found that crude casein, eggs,[40, 41] autolyzed yeast,[42] rice polishings and wheat germ could be substituted for beef muscle. In 1932 the resistance to autoclaving of the unknown factor in autolyzed yeast and its solubility in 70 or 80 per cent alcohol suggested a possible identity with vitamin B_2,[42] at that time synonymous with vitamin G and as yet unidentified with any chemical substance. Later, it was shown[43] that the extrinsic-factor activity of casein and of beef muscle was eliminated only by exhaustive extraction with dilute acetic acid or with alcohol, procedures known to remove members of the vitamin B complex. However, since these substances, including pteroylglutamic acid and its conjugates,[44] thereafter became identified as chemical entities, they were shown individually and in combination not to be the food (extrinsic) factor.[43] Eventually, in 1948, when vitamin B_{12} became available for such clinical studies it (cyanocobalamin)[45, 46]

and later vitamin B_{12a} (hydroxycobalamin)[47, 48] were found to acquire increased hematopoietic power when administered together with gastric juice in pernicious anemia. Formijne[49] had already demonstrated that suitably prepared 70 per cent alcohol-soluble extracts of beef muscle were effective as extrinsic factor. Microbial analysis now showed them to contain vitamin B_{12} in amounts sufficient to explain the hematopoietic effects observed when they were administered orally with gastric juice as well as when given intravenously alone.[50]

It thus belatedly became apparent that the anti-pernicious-anemia principle of purified liver extracts was also the so-called extrinsic factor. This identity might have become clear much earlier if, as pointed out by Dock,[51] parenteral administration of beef-muscle extracts had been pursued more actively. The positive result of the Klein and Wilkinson[52] experiments with intramuscular injections of extracts of beef muscle after incubation with extracts of hog-stomach mucosa is in retrospect probably attributable to the independent action of the vitamin B_{12} present. Our own observations were indeterminate, probably because of the relatively small amounts of beef-muscle extract that could be injected intramuscularly without discomfort to the patient. The situation was further obscured by our mistaken conclusion that hydrolysis with sulfuric acid destroyed the hematopoietic activity of a relatively crude liver extract upon parenteral injection but not its so-called extrinsic-factor activity. As early as 1931 Reimann[53] had demonstrated what proved to be a thirty-fold potentiation of liver by admixture with gastric juice, and this test for the presence of extrinsic factor had been shown by others to hold for a crude liver extract.[54] In 1948 we found that a purified liver extract for parenteral use also contained extrinsic factor and that hydrolysis with dilute sulfuric acid destroyed its extrinsic factor as well as its antipernicious-anemia activity upon parenteral injection. This fortunately prompted the successful trial of vitamin B_{12} as extrinsic factor with gastric juice.[45]

Why brewers' yeast is inert and autolyzed yeast active as extrinsic factor remains unexplained today despite the extensive studies of Wills,[55] Groen[56] and Ungley,[5, 57] among others. Available analyses for vitamin B_{12} do not indicate that it occurs in sufficient amounts in yeast to account for the effects formerly observed with gastric juice.[58] Perhaps the process of autolysis then employed in some way released vitamin B_{12} bound within living yeast cells or created it as a result of fermentation or bacterial contamination. The possibility of differences in the vitamin B_{12} content of the nutrient medium of different batches of yeast cannot be excluded.

Characteristics of the Intrinsic Factor

Early in the course of our studies it was shown that demonstration of the intrinsic-factor activity of normal human gastric juice required that the naturally buffered mixture of 200 gm. of beef muscle and 75 cc. or more of gastric juice then employed be given to the patient at a pH of not less than 5.[59] Moreover, the subsequent hematopoietic activity of such a mixture was found to be destroyed at once by boiling and within half an hour by a temperature of from 70 to 80°C. at pH 5 or 7 or by 70 per cent alcohol.[49] By analogy with other gastric functions it was assumed that this meant that some type of enzyme had been inactivated. Unlike pepsin, the intrinsic factor was shown by others[60, 61] not to be destroyed by exposure to alkali, and preparations of commercial pepsin derived from the hog were found to be ineffective.[59] Gastric juice freed from pepsin and rennin by casein precipitation was active.[62] Moreover, gastric juice containing hydrochloric acid, pepsin and rennin was obtained from rare patients with nutritional macrocytic anemia and found not to contain detectable amounts of intrinsic-factor activity.[63] Later, the intrinsic factor was shown by others to be unable to pass through an ultrafilter[62] or a dialysis bag, to be partially adsorbed by Lloyd's reagent and to be precipitated by half-saturation of gastric juice with ammonium sulfate.[64] Gratifying to the clinical investigator is the fact that gastric juice retains its intrinsic-factor activity after being passed through the Berkefeld V filter[46, 65] and after being kept frozen for many weeks or after lyophilization and reconstitution with distilled water.[66] These properties suggest a large molecule, presumably a protein, as the basis of intrinsic-factor activity.

Certain characteristics of gastric juice that have been claimed to be of possible significance in its intrinsic-factor activity deserve mention. In 1938 proteolysis of casein at pH 7.4 by normal human gastric juice was found by Taylor and his associates[65] to progress within twenty-four hours at incubator temperature chiefly to the stage of proteoses and peptones. Subsequently, this phenomenon was found to persist under most of the in vitro conditions known to preserve the clinical activity of the intrinsic factor.[65] Bonsdorff[67] subsequently reported such proteolysis to be inhibited by a protein-containing extract of the fish tapeworm. This parasite infests the upper small intestine of many persons in Finland, a few of whom acquire pernicious anemia while still able to secrete small amounts of hydrochloric acid, and presumably of intrinsic factor, in the stomach. The intrinsic factor has also been claimed without confirmation to be a prolinase.[68] Preparations of hog-stomach mucosa possessing strong alpha-aminopolypeptidase activity have been stated to possess intrinsic-factor activity when administered with derivatives of beef muscle in pernicious anemia.[69] However, subsequent observations[66] have failed to demonstrate intrinsic-factor activity with preparations derived from calf thymus

containing aminopolypeptidase. Moreover, normal human gastric juice has been found not to contain significant enzyme activity of this type. Likewise, the claim, apparently based on defective clinical observations, that lysozyme possesses activity as intrinsic factor has not been confirmed with the use of egg lysozyme.[69] Indeed, lysozyme is present in greater concentrations in the gastric secretions of patients with pernicious anemia than in those of the normal person.[70]

Glass and his associates[71] recently demonstrated intrinsic-factor activity in samples of glandular mucoprotein precipitated at pH 2 from clarified samples of the gastric juice of normal subjects. This substance is stated to possess the physical characteristics of intrinsic factor so far as these are known. The daily oral administration of 100 mg. of the mucoprotein preparation, together with 10 to 20 microgm. of vitamin B_{12}, did not produce optimal hematopoietic responses. These usually require 30 microgm. of vitamin B_{12} and 50 to 75 mg. of glandular mucoprotein. However, it appears more likely that intrinsic factor is associated with rather than identical with gastric mucoprotein because of the much smaller amount of material shown to possess intrinsic-factor activity by Welch and Heinle.[58] Extending the earlier observations of Helmer and his co-workers,[62] they made highly active preparations from a large pool of gastric juice kept frozen during the period of its accumulation. Their first procedure was to destroy the pepsin by exposure to pH 9. Then, after readjustment to pH 4.5, the precipitate resulting from full saturation with ammonium sulfate was dialyzed and redissolved in water. The solution was then adjusted to pH 1.5, the soluble material removed, and the supernatant, after readjustment to pH 4.5, half saturated with ammonium sulfate. After dialysis of dry material so obtained, the precipitate from each 100 cc. of original gastric juice was found to weigh 0.6 mg. Yet in a clinical test it was shown distinctly to potentiate the activity of 5 microgm. of vitamin B_{12} on daily oral administration to a patient with pernicious anemia who had received 5 microgm. of vitamin B_{12} daily during an immediately preceding ten-day period.

Further studies[72] of mucous substances in gastric juice by means of electrophoresis have demonstrated the presence of two mucopolysaccharide substances, "mucoproteose" and "glandular mucoprotein," both with highly negative charge. However, the former has a very slow, and the latter a fast mobility. Recently, Latner et al.,[73] using paper-strip electrophoresis of highly concentrated preparations of gastric juice in barbitone buffer at pH 8.6 or 6.35, demonstrated intrinsic-factor activity in an anode peak of material containing either a mucoprotein or a mucopolysaccharide. Another peak on the cathode side of the point of application to the paper strip contained more mucoprotein but less intrinsic-factor activity when clinically tested. The clinically active anode-peak fraction contained 40 mg. of material, but owing to the single-dose method of testing employed, comparison of this clinical activity with that of some of the American preparations referred to cannot be satisfactorily made. The latest report of Latner and Ungley[74] indicates that clinical activity has been noted with as little as 2 mg. of solid material derived from hog-stomach mucosa. Carbohydrate is present, as well as various amino-acids, not including lysine, histidine and tyrosine.

Sites of Secretion of the Intrinsic Factor

After the discovery, in 1928, of the hematopoietic effectiveness in pernicious anemia of mixtures of beef muscle and gastric juice, attempts were made to treat such patients with digests of hog-stomach mucosa incubated at pH 2.5 to 3.5 for seventy-two hours and subsequently brought to pH 5. Our[75] failure, which presumably resulted from destruction of the intrinsic factor during the prolonged acid digestion with pepsin, was shortly followed by the successful use by Sturgis and Isaacs,[76] and by Sharp,[77] of desiccated defatted preparations of whole hog stomach. No doubt, desiccation preserved the intrinsic factor and resulted in the excellent clinical activity of similar preparations studied by Wilkinson,[78] Snapper and du Preez[79] and others. Besides intrinsic factor the presence of a heat-resistant factor, which like that in beef muscle could be potentiated by normal human gastric juice, was demonstrated in hog-stomach mucosa.[80] This was undoubtedly vitamin B_{12}, which is now known to be present in beef muscle and hog stomach as well as in duodenal mucosa,[81] from which it can be removed by dialysis.

Meulengracht[82, 83] has shown the hematopoietic effect in pernicious anemia of preparations of various portions of the mucosa of the hog stomach and duodenum and has thus defined the site of secretion of intrinsic factor in that animal. Surprisingly enough, it is absent from the thick, pepsin-secreting fundus area,[61, 84] though present especially in the "pyloric-gland organ" and also to some extent in the cardia[82] of the hog stomach. Whether the hematopoietic activity claimed for the ileum[85] and even for the colon of the hog depends upon the active secretion or merely upon the passive adsorption of intrinsic factor is not clear. Similar clinical observations with material of human origin appear to demonstrate that, in contrast to the situation in the hog, the intrinsic factor is secreted principally by the widely distributed and more or less histologically similar glandular structure representative of much of the human stomach.[84] In man the pyloric portion, which somewhat resembles that of the hog, does not appear to be a very active site of intrinsic-factor secretion, and this area is not involved in the

type of atrophy of the secretory structure characteristic of the stomach in pernicious anemia.[86, 87] Normal human duodenal secretions not containing gastric juice, because of its exclusion by a pyloric balloon[88] or as a consequence of previous total gastric resection,[89-90] do not appear to contain intrinsic factor. However, possibly as a result of passive contact with gastric juice, desiccated preparations of normal human duodenum seem to contain intrinsic factor.[91] This is not so for similar preparations of jejunum and ileum in man. Although at one time the suggestion was made that the argentaffin cells might be the source of intrinsic factor, comparative studies of their distribution and of the distribution of intrinsic-factor secretion in man and in the hog lend no support to this idea.[92]

Therapeutic Mixtures of Intrinsic Factor with Vitamin B_{12}

Practical advantage was soon taken of the observation of Reimann[93] in 1931 that gastric juice potentiated the hematopoietic activity of liver upon oral administration. An efficient therapeutic product[93] resulted from the incubation and subsequent desiccation of mixtures of stomach tissue and liver extract — no doubt because it contained both intrinsic factor and vitamin B_{12}. Recently, members of the pharmaceutical industry in Europe as well as in the United States have found it practicable to develop fractions of hog stomach or duodenal mucosa that in daily dosage in milligram amounts effectively potentiate the hematopoietic activity of a few micrograms of added vitamin B_{12}.[94, 95] The methods employed in the manufacture of these products have not been reported. However, Welch and his associates[95, 96] have described the preparation of active concentrates of intrinsic factor by relatively simple procedures similar to those employed with gastric juice and discussed above. Although not electrophoretically homogeneous, the protein content of the final fractions was equivalent to 0.03 per cent of the original crude source: a commercial desiccated stomach preparation. This material was first extracted with a 2 per cent sodium chloride solution. The extract was subsequently adjusted to pH 9 and then to pH 1.5. The remaining soluble material was then submitted to fractional precipitation at pH 4.5 with ammonium sulfate at 35 (A), 55 (B) and 100 (C) per cent saturations. Yields were obtained of 210, 15 and 570 mg., respectively, of dry material from 50 gm. of original desiccated stomach. Of these the smallest fraction (B) was the most active clinically, 15 mg. causing distinct hematopoietic effects when given daily with 5 microgm. of vitamin B_{12} to a patient with untreated pernicious anemia. Daily doses of 3 mg. of this fraction also diminished the fecal excretion of radioactive cobalt given daily in the form of 0.5 microgm. of Co^{60}-labeled vitamin B_{12}. These studies were conducted on patients with pernicious anemia in complete remission.[97] Using this method Latner and Ungley[74] demonstrated activity with 2 mg. of material from hog-stomach mucosa, which is electrophoretically homogeneous at pH 6.4 and which they regard as mucoprotein in nature.

Physiologic Function of the Intrinsic Factor

It remains to discuss the uncertainties about how intrinsic factor acts. Present knowledge strongly suggests that it merely promotes the absorption of vitamin B_{12} and some of its congeners as such by the intestine and so into the blood stream. Thus, sources of intrinsic factor increase the hematopoietic activity of cyanocobalamin[5, 45, 46] in untreated anemic patients while diminishing the fecal excretion of radioactive cobalt when cyanocobalamin so labeled is given to patients with pernicious anemia in remission.[74, 97] The daily parenteral injection of 1 microgm. of vitamin B_{12} alone invariably has a greater hematopoietic effect than the daily oral administration of 1 to 5 microgm. of vitamin B_{12} together with 25 to 50 cc. of gastric juice.[96] Gastric juice does not appear to potentiate the activity of vitamin B_{12} when both are given together intravenously in amounts comparable to those showing such potentiation upon oral administration. Finally, Horrigan and his associates[99] have demonstrated that vitamin B_{12} injected into the bone-marrow cavity in pernicious anemia may produce *local* maturation of erythrocyte precursors without or before the appearance of such effects in other marrow sites. However, other observations suggest other possible theories concerning the nature of the action of intrinsic factor.

Interaction-Product Theory

Initially, it was thought that some type of essential interaction between beef muscle and gastric juice occurred within the alimentary tract.[27] Thus, increased hematopoiesis was observed when beef muscle and gastric juice were administered together with or without preliminary incubation or even when they were separated by an interval of as long as six hours.[80] This did not occur when the interval was as long as twelve hours. However, because boiling for five minutes always destroyed the activity of gastric juice, of beef-muscle and gastric-juice mixtures, or even of such mixtures after subsequent incubation with human duodenal juice and thereafter with hog-intestine mucosa, it was concluded that the thermostable antipernicious-anemia principle in liver was not produced under these conditions.[59] At that time the formation of some intermediate compound of less thermostability than the active principle of purified liver extract could not be excluded. Today, because of the apparent identity of this principle, the extrinsic factor and vitamin B_{12}, these observations are interpreted to mean only that boiling destroyed the intrinsic factor. Al-

though a twelve-hour incubation period at pH 2.5 of a naturally buffered mixture of 200 gm. of beef muscle and gastric juice did not destroy its hematopoietic effect when the mixture was brought to pH 5 immediately before it was given to the patient, without such partial neutralization, the originally acid mixture was inert.[59] At the time this observation suggested the conclusion that an essential interaction between the two substances required a nearly neutral environment. At present, however, it is not known whether the clinical inactivity of the buffered acid mixtures implies an inhibitory effect of acid upon a process involving the intrinsic factor, the vitamin B_{12} or the superficial epithelial layer of the small intestine. One may, nevertheless, safely infer from such observations that the process of absorption of vitamin B_{12}, in whatever manner facilitated by intrinsic factor, normally takes place relatively high up in the small intestine and before the alkaline intestinal juices could have effectively reduced the acidity of the experimental mixtures.

A similar conclusion is suggested by clinical observations in patients with pernicious anemia caused by the fish tapeworm, in whom the administration either of beef muscle or vitamin B_{12} together with gastric juice may have no hematopoietic effect until the worm is expelled. In definitely anemic patients of this type the parasite was found (by intubation studies) to be in the jejunum.[100] On the other hand in worm carriers with other types of anemia the parasite was uniformly found in the ileum. Finally, displacement of the parasite from its usual habitat in the upper small bowel to a more inferior location may result in a remission of the macrocytic anemia even though the worm appears to have accommodated itself to life at a lower intestinal altitude. Whatever the mechanism by which the worm interferes with the absorption of vitamin B_{12} it appears that such an action is favored by the presence of the worm in the upper small bowel. The effectiveness of the oral administration of vitamin B_{12} with gastric juice in gastrectomized patients who have acquired pernicious anemia indicates that the stomach is clearly not an important site for its absorption.[89, 90] Studies with labeled cyanocobalamin suggest the same conclusion.[90]

Vitamin B_{12} Binding Theory

In 1949 Ternberg and Eakin[101] showed that normal human gastric juice contains a nondialyzable, heat-labile substance that combines stoichiometrically with vitamin B_{12}. Vitamin B_{12} bound in this fashion was found to be no longer dialyzable or able to support the growth of micro-organisms. This binding capacity of gastric juice for vitamin B_{12}, approximately 25 microgm. per 1500 cc.,[8] they proposed, without submitting clinical evidence, as a measure of intrinsic-factor activity. However, despite this lack of support the idea has been widely applied[102-104] in studies of gastric juice and other sources of intrinsic factor. Burkholder[105] believes that certain strains of coliform bacilli isolated from the upper intestinal tract of patients with pernicious anemia may be especially specific. Latner and his associates[73] have shown with paper electrophoresis that two peaks of vitamin B_{12} binding material from gastric juice possess intrinsic-factor activity. However, determinations based on this potentially useful guide for the laboratory quantitation of intrinsic factor do not correlate satisfactorily in the hands of some observers with the results of clinical tests. Perhaps this is not to be expected because several different proteins without intrinsic-factor activity as determined by clinical means have been shown to be capable of binding vitamin B_{12}.[106] Consequently, even if intrinsic factor possesses binding capacity this property may be obscured by other substances present in its native sources. Actual clinical tests have shown that poor or even inverse correlation may exist between the binding capacity for vitamin B_{12} of extracts of hog-stomach mucosa and their intrinsic-factor activity.[46, 96] The extensive observations of Everse, Lens and Wijmenga[94] to this effect include also tests of fractions of gastric juice.

It has been claimed that intrinsic factor after incubation with beef muscle[52] becomes more heat stable. With vitamin B_{12} the combination is also stated to be resistant to digestion with trypsin.[100] Nevertheless, in our[59] earlier observations boiling for five minutes invariably destroyed the activity of mixtures of beef muscle and gastric juice that had subsequently been submitted to digestion with trypsin-containing duodenal contents. Spray[107] has demonstrated a combination between vitamin B_{12} and something in neutralized gastric juice in which the vitamin B_{12} was unavailable to bacteria before prolonged boiling. However, after only twenty minutes at 95°C. (a temperature sufficient to destroy uncombined intrinsic factor) the clinical activity in pernicious anemia of the combination was found to be no greater than that of the contained vitamin B_{12}. Therefore, it appears to be unwise to equate vitamin B_{12} binding capacity as determined microbiologically with intrinsic-factor activity as determined clinically.

The demonstrated capacity of normal human gastric juice to render vitamin B_{12} unavailable to micro-organisms[101, 107] has naturally been assumed to indicate a possible basis for its physiologic function in man. Thus, it has been proposed that the action of intrinsic factor is based on its ability to protect the vitamin B_{12} needed by the patient from being utilized competitively by intestinal bacteria or by the fish tapeworm when harbored by such persons. Consistent with such an idea is the apparent ability of antibacterial substances capable of modifying the intestinal bacterial flora (chlortetracycline and penicillin) to produce hematologic remissions in pernicious

anemia[108, 109] although this does not always follow even with simultaneous oral administration of vitamin B_{12}.[8] Also consistent is the well known beneficial effect on the associated macrocytic anemia of the elimination of the fish tapeworm.[100] Presumably as a result of passive absorption or of utilization of preformed vitamin B_{12}, both colon bacilli[105, 110] and the tapeworm[111] are known to contain considerable amounts of vitamin B_{12}. Indeed, the parenteral injection of a suitable extract of the tapeworm[112] or the oral administration of dried powdered tapeworm together with gastric juice[111] produces hematopoietic remissions in pernicious anemia. When applied to addisonian pernicious anemia this hypothesis revives on a new basis the former concepts of intestinal sepsis of Hunter,[23] Hurst[22] and others.[24, 113] What is difficult to know from presently available information is whether there is a sufficiently numerous bacterial flora sufficiently high in the small intestine in pernicious anemia to be able to deprive the patient of the necessary amount of vitamin B_{12}.[4, 113, 114] The observation that the oral administration of even large doses of vitamin B_{12} may produce only slight hematopoietic responses in many patients weakens the case for the vitamin B_{12} binding theory because the organisms presumably could remove only a small proportion of the vitamin so administered.[97] The effect of antibiotics may be due to the increased production of more readily absorbed hematopoietic substances such as citrovorum factor[6] or even to the elimination of "toxic" influences derived from intestinal bacteria.

Activated Vitamin B_{12} Theory

Another possible mechanism of action of intrinsic factor that would perhaps be consistent with its ability to bind vitamin B_{12} is the formation of a hematopoietically more active complex with cyanocobalamin. Even if so, the decreased fecal excretion of radioactive cobalt resulting when the cyanocobalamin so labeled was administered together with intrinsic factor by mouth would suggest that the combination of these factors was also more readily absorbed by the intestinal mucosa than was the vitamin alone.[90, 97] Moreover, as opposed to enhanced absorption of vitamin B_{12}, to date no evidence is available that, strictly speaking, the cyanocobalamin molecule is rendered hematopoietically more active by contact with intrinsic factor. The reported lack of change in the spectroscopic properties of the vitamin B_{12} molecule upon incubation with gastric juice does not exclude such a possibility because much of the relatively large amount of vitamin B_{12} employed may have remained unbound.[115] The apparent effect of gastric juice in activating vitamin B_{12} in bone-marrow cultures[116] in pernicious anemia could indicate either an effect on cell permeability or the formation of a more potent vitamin B_{12} complex.

Whatever the mechanism involved, 10 cc. of Berkefeld-filtered gastric juice may distinctly enhance the hematopoietic activity of 1 microgm. of vitamin B_{12} upon simultaneous daily oral administration.[90] However, it was not possible to demonstrate any consistent increase in the hematopoietic activity in pernicious anemia of 0.33 microgm. of vitamin B_{12} after incubation with 10 cc. of sterile gastric juice when such mixtures were given daily *intravenously*.[98] The intravenous route was employed to exclude the demonstrated effect of intrinsic factor in promoting the absorption of vitamin B_{12} when these substances are given together by mouth.[97] It has recently been reported that vitamin B_{12} when given by inhalation was hematopoietically effective and that the urinary excretion that occurred was even greater than when similar amounts of vitamin B_{12} were given by mouth.[117] This suggests that contact with intrinsic factor is not an indispensable step in the absorption of vitamin B_{12} through a mucous membrane and that the cells of the intestinal mucosa are not uniquely permeable to contact with vitamin B_{12}.

Catalyzed Absorption Theory

The most probable mechanism of action of intrinsic factor assumes that it directly and specifically facilitates the absorption of vitamin B_{12} by the intestinal wall. The decreased fecal excretion of radioactive cobalt that results from the oral administration of intrinsic factor together with cyanocobalamin so labeled clearly suggests this inference.[97] In contrast to vitamin B_{12} no detectable difference in the absorption of single doses of glucose, tyrosine, casein or pteroylglutamic acid is observed on oral administration whether with gastric juice or with an equal volume of physiologic salt solution.[80] The acute and apparently specific effect of intrinsic factor upon the absorption of vitamin B_{12} is, of course, not to be confused with the more gradual improvement in the ability of the intestine to absorb glucose[118] and other nutrients after effective treatment. However, this result of vitamin B_{12} deprivation may well be superimposed for this vitamin upon the specific absorption defect created by lack of intrinsic factor.[93]

The significant relation is thus perhaps not so much between intrinsic factor and vitamin B_{12} as between intrinsic factor and the intestinal mucosa.[80] According to this view, the requirement of a relatively neutral intestinal environment for the action of intrinsic factor suggests that possibly it catalyzes some enzymic process in the superficial layer of the epithelium of the upper small-intestine wall that is in turn directly concerned with the absorption of vitamin B_{12}. The activation of one enzyme system by another is a phenomenon familiar to biochemists and to students of intestinal enzymes.[119] At least consistent with this idea is the fact that when intrinsic factor is orally administered to a patient four

hours before an equal volume of a solution of vitamin B_{12} a greater hematopoietic effect is observed than when the order of administration of these substances is reversed.[98] This hypothetical "facilitating effect" of intrinsic factor is a transient one because the hematopoietic potency of vitamin B_{12} is not enhanced if its administration follows that of the gastric juice by an interval of as long as twelve hours.[48] Moreover, in contrast to the stoichiometric relation between gastric juice and the amount of vitamin B_{12} bound against microbial utilization in vitro[101] is the clinical evidence for a reciprocal relation observed by Glass and his associates.[71] In our observations, also, when suboptimal daily dosages of these substances were given together by mouth to patients with pernicious anemia a greater hematopoietic effect was subsequently achieved by a sufficient increase of either. Thus, it was shown that 10 cc. of normal human gastric juice would detectably potentiate the activity of 1 microgm. of vitamin B_{12}. However, the hematopoietic effect was not so great as when either 5 microgm. of vitamin B_{12} was given with 10 cc. of gastric juice or 25 cc. of gastric juice was given with 1 microgm. of vitamin B_{12} during successive periods of observation in the same patient.[99] Nor were any of these combinations given by mouth as active as the daily intramuscular injection of 1 microgm. of vitamin B_{12}.

The demonstration by Heinle and his associates[97] of the decreased excretion of radioactive cobalt after the simultaneous oral administration of intrinsic factor together with cyanocobalamin so labeled clearly suggests that increased amounts of cyanocobalamin are being absorbed as such. It is a most important improvement over existing clinical methods of assay of intrinsic factor. When this observation is considered together with the enhanced hematopoietic action of vitamin B_{12} under these circumstances and its failure to be rendered more active by gastric juice upon intravenous injection the conclusion seems inescapable that the action of intrinsic factor consists in a specifically enhanced intestinal absorption of vitamin B_{12}. As a next step it appears logical to attempt to develop methods of in vitro study of the transport of vitamin B_{12} across cell membranes. Indeed, this is possibly the basic process involved in the recently reported studies of Lajtha and Callender.[116, 120] Using cultures of bone marrow from patients with untreated pernicious anemia, they first noted that the megaloblasts disappeared when normal serum was added, but that this did not occur to a comparable extent with pernicious-anemia serum. Vitamin B_{12} when added did not cause "ripening" of the megaloblasts unless a small amount of sterile unheated gastric juice was also added. This suggested that the gastric juice was effective either by forming a potent hematopoietic factor with vitamin B_{12} or by counteracting the effect of an inhibitor of this process that was present in the serum of the patient. Callender and Lajtha[116] extrapolate these experiments to the patient to indicate that the transport of vitamin B_{12} across the intestinal membrane requires a gastric intrinsic factor and that its utilization by the cells of the bone marrow requires an "extra-gastric intrinsic factor" that is present in normal serum. In the bone-marrow cultures in pernicious anemia, gastric intrinsic factor is assumed to be able to replace the theoretically absent or inhibited extragastric intrinsic factor of normal serum. However, despite confirmation of the inactivity of vitamin B_{12} in such bone-marrow preparations,[121] it is difficult to reconcile these conclusions with the in vivo demonstration of Horrigan and his associates[99] of a local megaloblast maturing effect from the instillation of vitamin B_{12} *alone* into the bone marrow.

Admittedly, both types of experiments are technically difficult, especially the preservation of the morphologic characteristics of cells in bone-marrow cultures. From the studies of Mollin and Ross,[122] with the *Euglena gracilis* method,[123] it is clear that the vitamin B_{12} in normal serum is combined with one or more of its heat-labile components. Perhaps such a carrier is necessary for the transport of the vitamin B_{12} from the intestinal tract to the bone marrow, and its lack may have conditioned a failure of the vitamin B_{12} to reach the bone marrow in an effective form in the extraordinary patient described by Horrigan and Heinle.[124] On the other hand Lear[125] has found no consistent difference from normal in the proportions of bound and unbound vitamin B_{12} in the serum of most patients with pernicious anemia after the in vitro addition of sufficient vitamin B_{12} to raise its total concentration to normal levels. There thus appears to be no obvious reason why gastric juice should be required for the maturation of bone-marrow megaloblasts in vitro any more than in vivo.

Conclusions

I am sure that there is now general agreement at least on the present state of uncertainty about the nature and function of the intrinsic factor. What is obviously needed is not more theories but more facts. The necessity for resort to clinical trial of therapeutic effects in patients with pernicious anemia has long been a serious impediment, as in the identification of the antipernicious-anemia principles of liver: folic acid and vitamin B_{12}. Those problems were finally solved by members of the pharmaceutical industry, who channeled a confluence of information provided by technical advances chiefly in microbiology and chromatography to successful confirmation by clinical trial. It may confidently be expected that the solution of the problem of the nature of this unknown component of gastric juice when reached will likewise depend upon a correlation of new laboratory methods with the now con-

ventional clinical studies. It is to be hoped that this scientific goal, which has been viewed so long from a distance, is now close at hand.

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MEDICAL INTELLIGENCE

CLINICAL AND INVESTIGATIVE APPLICATION OF A NEW INSTRUMENT FOR CONTINUOUS RECORDING OF BLOOD PRESSURE AND HEART RATE*

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WASHINGTON, D. C.

IN both routine hospital practice and clinical investigation, there has long been a need for an instrument that will continually record blood pressure and heart rate without discomfort to the patient.

The instrument used in the present study was designed and constructed by Gilford and his associates.[1] This "physiologic monitor" is primarily intended for use by the anesthesiologist, providing him with a continuous record of the patient's blood pressure, heart rate, respiratory rate and minute respiratory volume, at the same time freeing him for other and occasionally more urgent duties in the operating room. The monitor also provides an instantaneous indication of the occurrence of arrhythmia and supplies an outlet for convenient recording of the electrocardiogram. The present report is concerned with the preliminary evaluation of the blood-pressure and pulse recording components in medical ward patients.

The blood pressure is automatically measured by a modification of the conventional auscultatory method. A microphone pickup is placed over the brachial artery and covered by a standard inflatable arm cuff (Fig. 1). An air compressor slowly inflates the cuff. The first pulse beat picked up by the microphone activates a diastolic-blood-pressure indicator. Inflation of the cuff continues until the pressure within it rises to a level 10 above the last recorded pulse beat. At this level the pressure in the cuff automatically releases slowly until the first pulse beat detected by the microphone actuates the systolic-blood-pressure indicator. Pressure in the cuff is then immediately released to 0. The diastolic and systolic pressures are recorded on a Speedomax chart (Fig. 2), which can be located at any distance from the patient. The measurement cycle is repeated every three minutes.

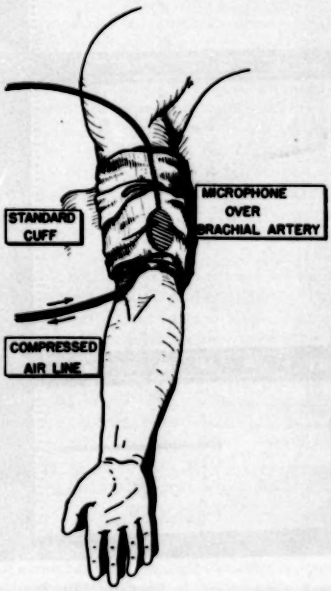

FIGURE 1. *Sketch Showing Application of the Microphone Pickup beneath a Standard Type of Pneumatic Arm Cuff. The skin beneath the microphone is painted with tincture of benzoin, and the microphone is fixed in place by means of adhesive tape of the elastic type ("Elastoplast") before the application of the pneumatic cuff.*

Two safety valves, one electric and one mechanical, prevent excessive inflation of the cuff. The level of the microphone signal can be regulated by a gain control so that only true pulse beats are detected and extraneous noise occasioned by the patient's movements in bed does not influence the recording. The apparatus produces no more discomfort than manual inflation of a cuff and does not interfere with sleep.

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Heart rate is measured continuously by means of an electronic circuit that times the interval between "R" waves, using standard electrocardiographic

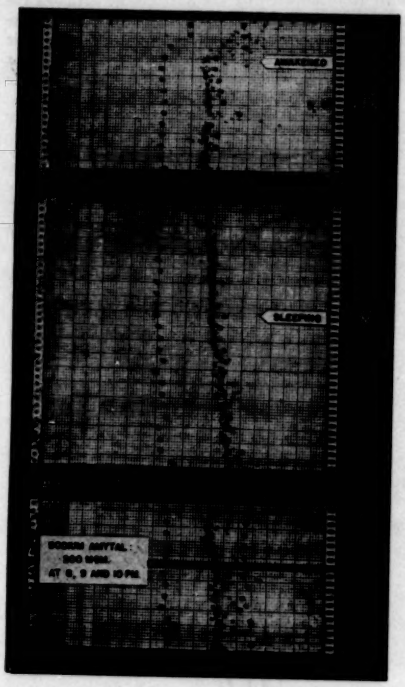

FIGURE 2. *Cuttings from the Speedomax Chart Recordings in Case 1.*

Two hundred milligrams of Sodium Amytal was administered orally at 8, 9 and 10 p.m. Systolic and diastolic pressures have been circled to make them stand out in the black-and-white illustration. (Systolic is on the right, and diastolic on the left.) The recordings not circled represent the heart rate.

electrodes. This information is recorded every thirty seconds on the Speedomax chart.

On the wards this instrument has been left unattended for long periods while a printed record of blood pressure and pulse was automatically recorded. The period of continuous operation has been as long as twenty-one hours. Patients have been able to feed themselves and move about in bed.

ILLUSTRATIVE CASES

Twenty tests were carried out. These included 4 recordings of blood pressure and heart rate through the night during normal sleep or after the standard doses of Sodium Amytal used in the "sedation" test. Other patients included 3 with acute gastrointestinal hemorrhage, 1 with sinus tachycardia, 1 with postrenal biopsy and 11 with hypertension in whom the effects of hypotensive drugs were observed. The following cases illustrate the type of information derived from the instrument.

CASE 1. M. S., a 50-year-old man with essential hypertension, was given 0.2 gm. (3 gr.) of Sodium Amytal at 8, 9 and 10 p.m. Recording began at 6 p.m., when the blood pressure was 215/105 and the pulse 78 (Fig. 2). The patient fell asleep and awoke

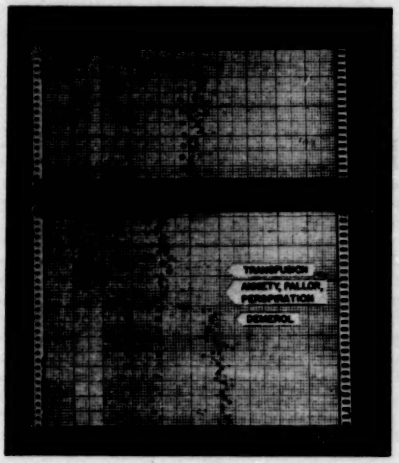

FIGURE 3. *Cuttings from the Speedomax Chart Recordings in Case 2.*

Other notations are similar to those in Figure 2.

during the early evening, with abrupt changes in blood pressure, but near 1 a.m. he again slept with a more gradual fall in blood pressure (Fig. 2) to a level of 160/85. He awoke 3 hours later, when the record showed an abrupt increase of blood pressure from 160/85 to 185/120 and of pulse from 68 to 76. The elevations occurred in a 5-minute period. The rapid blood-pressure changes, with falling asleep and awakening, were seen in several other cases.

CASE 2. R. H., a 60-year-old man with a past history of peptic ulcer, entered the hospital because of the recent onset of hematemesis and tarry stools. Recordings began at 5 p.m., when the blood pressure was 80/50 and the pulse 75 (Fig. 3). At 5:25 p.m. the patient was given 50 mg. of Demerol subcutaneously. Three minutes later the blood pressure and pulse began to fall, and 6 minutes after the drug had been given the blood pressure was 65/40 and the pulse 52. The nurse who noted this sudden change in the record found the patient to be anxious, pale and sweaty. A transfusion of 500 cc. of blood was given, after which the blood pressure rose slowly to 110/50 and the pulse to 68. No further changes occurred for the remainder of the night.

This incident probably represented a vasovagal attack induced by the injection of Demerol in a patient who had incipient shock.

CASE 3. F. T., a 55-year-old man with essential hypertension, was under treatment with parenteral injections of hexamethonium 3 times daily. It seemed of interest to record his response to the medication. Before injection the blood pressure was stabilized at 215/130 (Fig. 4). Three minutes after subcutaneous injection of 100 mg. of hexamethonium, the blood pressure had fallen to 180/125. The maximum effect of the drug occurred 15 minutes after the administration of hexamethonium, when the blood pressure was 160/110. At 1 hour, the blood pressure was 170/125, and at 2 hours it was 185/125. At 3 hours it was 180/130, but at 4½ hours it rose to 250/130. Thus, a detailed record of the onset, degree and duration of the hypotensive effect was obtained, indicating a surprisingly rapid onset of effect and a duration of 4½ hours with the patient in the supine position.

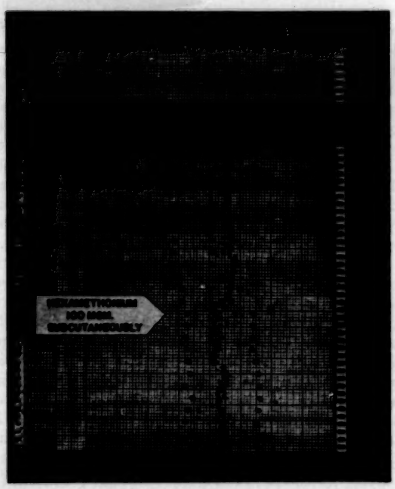

FIGURE 4. *Cuttings from the Speedomax Chart Recordings of Case 3.*

Other notations are similar to those given under Figure 2.

DISCUSSION

It should be emphasized that the instrument described above was constructed for use in anesthetized patients in the operating room. The present study explored the use of the apparatus in ward patients. A much simpler instrument would be adequate for such purposes since only blood pressure and pulse were recorded.

Difficulties were occasionally encountered with the electrocardiographic leads from which the heart rate was recorded. Increased activity on the part of the patient at times produced interference with proper recording, and the leads occasionally became loose. However, for the present purpose it seems possible that the heart rate could be recorded directly from the microphone pick-up used for determining blood pressure, thus eliminating the electrocardiograph leads.[2]

Blood-pressure measurement was attended with few difficulties. One patient complained of discomfort severe enough to require removal of the cuff. Painting of the skin under the microphone with tincture of benzoin and slight lubrication of the microphone prevented severe pressure marks on the skin during long test runs.

Our experience with the "physiologic monitor" has indicated that an instrument of this type that will provide continuous, quantitative recordings of blood pressure and pulse is of considerable value in routine hospital practice and in clinical investigation. In clinical practice remote positioning of the recorder permits the nurse to observe pressure and pulse changes from her desk in acutely ill patients. The investigator can obtain a permanent record of these physiologic variables in response to drugs or other procedures. Further developments in this type of apparatus, now in progress, should lead to instruments suitable for general hospital use.

SUMMARY

A "physiologic monitor" for the automatic recording of a number of physiologic variables is described. Although primarily designed for operating-room use, it has been shown, by preliminary testing on the medical wards, to be useful for the blood-pressure and pulse recording in ward patients. Illustrative cases and recordings are presented.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39411

PRESENTATION OF CASE

A fifty-five-year-old Italian laborer was referred to the hospital with a diagnosis of rheumatic heart disease and auricular fibrillation.

At the age of twenty-seven the patient spent one month in a hospital because of swollen legs and abdomen. He was told he had "leaky valves" and a large liver. He was digitalized then and maintained over the ensuing twenty-eight years on 0.1 gm. a day. He denied symptoms of rheumatic fever but had had frequent epistaxes at the age of five. He worked hard as a laborer, mixing cement and lifting heavy objects without undue dyspnea, until six months before admission, when he noted easy fatigability and vague aches developed especially over the precordium, occurring three or four times a day and lasting half an hour to two hours. These aches were not related to meals, exertion or breathing, and two months before entry they spread to the right side of the chest. He also noted pain in the lower midportion of the back, as though someone had hit him with a stick, and complained of pain across the lower anterior ribs, mostly at night when he was moving in bed. He had no joint or ankle swelling and no palpitation, and as before was able to climb 2 or 3 flights of stairs without shortness of breath. His physician noted hepatomegaly and gave him mercurial diuretics. Digitalis was increased to 0.2 gm. a day for a three-week period but was reduced because of nausea. He had lost 2 or 3 pounds from his usual weight of 155 pounds. He noted a slight increase in his usual cigarette cough six months before admission but had no hemoptysis. There were no sore throats. He thought he had been "jumpy" or "nervous" for the past six months, and sweated more days and nights without known fever. He preferred cold weather, using only 1 thin blanket during the previous winter. Five days before admission, he was seen by a cardiologist, who noted a very slight rumble at the apex, auricular fibrillation (rate of 150), decreased breath sounds at the left base medially and a liver that extended to the umbilicus.

Physical examination showed a thin, moderately hyperactive man who was sweating profusely, with slight dyspnea on exertion and a nonproductive cough. His skin was warm and pliable, and there was a slight tremor of the outstretched hands. The eyes were not prominent; no lid lag was noted. The neck veins were flat with the patient sitting; no thyroid tissue was palpable; the trachea was in the midline. The chest had a few high-pitched wheezes and occasional rhonchi at the left base medially. The heart was enlarged, the border extending 5 cm. to the left of the midclavicular line in the seventh intercostal space, with a totally irregular rhythm at 130 to 140. There was a high-pitched, whiny, Grade 2, moderately short apical systolic murmur. The aortic second sound equaled the pulmonic. No diastolic murmur was heard. The abdomen was rounded, with a slightly tender liver edge felt 10 cm. below the right costal margin. No other masses were felt. There was no peripheral edema. Neurologic examination was negative.

The temperature was 98.6°F., the pulse 130 to 140, and the respirations 20. The blood pressure was 130 systolic, 85 diastolic.

Examination of the blood showed a white-cell count of 14,000, with 81 per cent neutrophils. The hemoglobin was 13.5 gm. per 100 cc. The sedimentation rate was 42 mm. per hour. Urinalysis was negative. An electrocardiogram demonstrated auricular fibrillation at a rate of 120, a sagging ST segment in Leads 2, V_5 and V_6; deep S waves in Leads V_2 to V_4, tall R waves in Lead V_5 and occasional ventricular ectopic beats. The serum electrolytes were normal. The blood Hinton test was negative. An x-ray film of the chest revealed an enlarged heart with a cardiothoracic ratio of 18:31 (Fig. 1). The enlargement was predominantly of the left ventricle, with enlargement of the left atrium and well marked prominence of the pulmonary artery. No calcification was seen on fluoroscopy. A poorly defined, diffuse density present in the left lower lobe was associated with pleural effusion.

On the second hospital day the patient coughed up bright-red blood-tinged sputum and complained of pain in both right and left sides of the chest. He had some pain and a "jumping sensation" in the right hip and leg but no calf tenderness or swelling. Two days later there was pleuritic pain in the right side of the chest anteriorly, and coughing led to shooting pains down the right leg. On the sixth hospital day a pleural friction rub was heard over the left side of the chest posteriorly that persisted for four days, with daily blood spitting, which was intermittent during the entire hospital course.

Sputum culture grew out abundant pneumococci with a moderate number of *Haemophilus influenzae*. Dicumarol was begun, and the prothrombin time was maintained at 14 to 30 per cent of normal.

Films of the lumbar spine revealed a spina bifida of the fifth lumbar vertebra, with a plate of bone formed from the spines of the fifth lumbar to the first sacral vertebra. A lumbar puncture showed

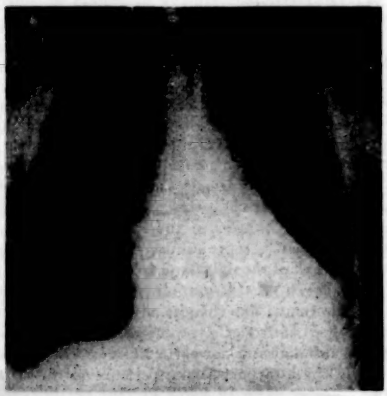

FIGURE 1.

normal spinal-fluid pressure and dynamics; examination of the spinal fluid was negative. A myelogram was normal.

On the thirteenth hospital day, blood spitting recurred, and the patient complained of pain over the left lower side of the chest. There were dullness and decreased breath sounds on the left, with a palpable axillary friction rub. A chest roentgenogram at this time showed a slight increase in fluid at the left base. On the twenty-sixth hospital day radioactive iodide studies showed 79 per cent uptake in forty-eight hours (normal 20 to 50 per cent). A thoracentesis yielded 250 cc. of grossly bloody, nonclotting fluid with a specific gravity of 1.009; there were 1800 red cells and 6000 white cells per cubic millimeter, with 90 per cent lymphocytes, 6 per cent neutrophils and 2 per cent monocytes. Cytologic study for tumor cells was reported as doubtful. Another left-sided thoracentesis two days later yielded 200 cc. of fluid with similar laboratory findings. During the thirtieth hospital day, the pulse rose to 172, and there was increasing orthopnea, dyspnea and apprehension. The temperature rose to 103°F. by rectum, and there were decreased breath sounds and moist rales at the right base. A repeat electrocardiogram showed no changes; the chest film demonstrated still more fluid in the left side of the chest and a soft, diffuse density in the right lower lobe, with a slight increase in the density at the left lower lobe (Fig. 2). The patient died on the thirty-fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD F. BLAND*: When I first read this case summary a day or so ago, it seemed the straightforward story of a patient who, in spite of long-standing rheumatic heart disease, had been quite well over the years. The severe illness twenty-eight years before admission, when the diagnoses of a leaking valve and congestive heart failure were made, sounds like the onset of severe rheumatic

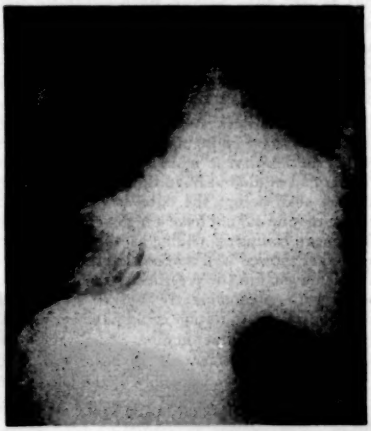

FIGURE 2.

fever that quieted down and left him with only minimal heart disease. He was able to work vigorously and hard without trouble until six months before he entered the hospital. He then began to have shortness of breath, which one can assume represented the onset of his auricular fibrillation. This was about the right age for such an occurrence in a patient with rheumatic heart disease. It was at first not too well controlled; some congestion developed, and he began to have pulmonary infarcts, which are very common in rheumatic heart disease with congestive heart failure, and he died as a result of a combination of rheumatic heart disease, auricular fibrillation, pulmonary infarcts and congestive heart failure. That sequence seems quite convincing until one begins to examine some of the details.

*Physician, Massachusetts General Hospital.

In the first place, whatever else he had, he must have had pulmonary infarcts in the lungs either from clots or from tumor cells. The difficulty encountered in controlling the heart rate, the intermittent hemoptysis with pleural pain, the evanescent shadows first on one side of the chest and then on the other and the bloody fluid, especially since it was a left-sided effusion, all speak in favor of pulmonary infarcts.

Where did the emboli originate? The heart was fibrillating, but I have considerable difficulty here in making a diagnosis of mitral stenosis. A cardiologist found a slight diastolic rumble at the apex, but after thirty days' study in the hospital an unimpressive apical systolic murmur remained as the only physical sign upon which to base a diagnosis of valvular disease. I do not know how to reconcile this paucity of findings with mitral stenosis, and there are other findings against that diagnosis as well as against congestive heart failure. How can a patient have a liver enlarged to the umbilicus from congestive heart failure and yet have no swelling of the neck veins? Distended neck veins are sometimes overlooked, especially the pulsations of the deep jugular veins, but after thirty days in the hospital it must have been clear that he either had or did not have a high venous pressure and so I shall accept the data as recorded as indicating that he did not have a high venous pressure.

The next confusing finding is that the electrocardiogram showed well marked left-axis deviation, which is unusual in the presence of rheumatic heart disease with predominantly mitral stenosis, although mitral regurgitation could have caused such an electrocardiographic finding. The radiologists said that the enlargement of the heart was chiefly of the left ventricle and possibly of the left atrium. I think at this point we had better get some help from the radiologist.

DR. JOSEPH HANELIN: The chest films were all made during the patient's hospital stay and extend over a month's time. The initial films made here, consisting of posteroanterior, lateral and right and left anterior oblique views, demonstrate a considerably enlarged heart, predominantly in the region of the left ventricle although there may be some increased size of the left atrium as well (Fig. 1). The esophagus is displaced posteriorly in the region of the left ventricle and perhaps to some degree in the region of the atrium, but this is not the typical heart of mitral stenosis and the cardiac configuration primarily suggests enlargement of the left ventricle. The right lung is clear. There is prominence of the left-lung root. The density described at the left base is best shown in the left anterior oblique view, and is not too sharply outlined, as was mentioned, but is quite definite. There is a small amount of pleural fluid.

DR. BLAND: Can you point out "Hanelin's sign"* of a large obstructed pulmonary vessel with a relatively avascular lung beyond it?

DR. HANELIN: Not in this case. A set of films five days later shows some further increase of the density in the left lower lobe; otherwise, there is no particularly noticeable change.

DR. BLAND: Do you think that infarcts would expand in the lung? I was not aware that they would.

DR. HANELIN: The same infarct would not.

DR. BLAND: Perhaps we see two infarcts together.

DR. HANELIN: Unless there is an infarct and pneumonia combined, I should not expect the infarct per se to enlarge. A grid film about two weeks after the initial examination shows a rounded density overshadowing the lower mediastinum on the right that is not typical of the left atrium and makes one wonder about some adenopathy. There is also a question of subcarinal adenopathy. The last examination of the chest shows considerable further increase of the process in the left lower lobe and development of a more diffuse type of density in the lower half of the right-lung field (Fig. 2).

DR. BLAND: What is that?

DR. HANELIN: The changes on the right have the appearance of some type of acute pneumonic process although it is not particularly characteristic. I would think of pneumonia, perhaps on the right side.

DR. BLAND: You think it is not circulatory in the sense of pulmonary edema?

DR. HANELIN: I think pulmonary edema could be playing some part in this picture. We do see localized edema at times that may resemble the change in the right lung. I should expect generally to see more associated change in the upper portion of the lungs. Pulmonary congestion may be responsible for the picture, but in addition, I wonder if there is not a superimposed acute pneumonia at the right base. The films of the spine and the myelogram show no significant changes. There is a congenital abnormality of the spine that is probably not very important.

DR. BLAND: Are these pulmonary infarcts?

DR. HANELIN: I cannot be sure.

DR. BLAND: Could there be something around the heart in the pericardium that made it look large?

Was there anything wrong with this patient's thyroid gland? The gland was not palpable and was not seen on x-ray examination. The uptake of radioactive iodide was 79 per cent, which is quite high. There are conditions other than thyrotoxicosis that may elevate the uptake; perhaps I had better ask one of the experts to comment on the radio-

*Hanelin, J., and Eyler, W. R. Pulmonary artery thrombosis: roentgenographic manifestations. *Radiology* 56:689-703, 1951.

active iodide uptake. A few clinical signs suggested thyrotoxicosis — the difficulty in controlling the fibrillation, the rather silky skin and the fact that he disliked the heat. Dr. Maloof, do you want to explain the 79 per cent uptake?

DR. FARAHE MALOOF: A high uptake of radioactive iodide by the thyroid gland means only that the gland is avid for iodide; it does not mean thyrotoxicosis. The fact that a goiter was not palpable is somewhat against the diagnosis. Other conditions will increase the radioactive iodide uptake. Young girls around the onset of puberty apparently grow a small goiter for some reason and may have a high uptake of radioactive iodide. Certainly, most of these persons do not have thyrotoxicosis. More and more drugs are being found that are goitrogenic and cause an increased uptake. One of the drugs being used for hypertension, potassium thiocyanate, if given long enough will produce a goiter. When the drug is stopped, the radioactive iodide uptake may be high. I think it was Dr. Earle M. Chapman who suggested, years ago, the use of this drug for hyperthyroidism. We found that the nitrates, such as erythral tetranitrate, may cause an increased uptake. Butazolidine, the drug used in treatment of arthritis, and one of the asthmatic preparations (Felsol) cause a high uptake of radioactive iodide. An asthmatic patient, on Felsol, entered the hospital because of enlargement of the thyroid gland to seven or eight times the normal size, with a superimposed bruit and a palpable thrill. The forty-eight-hour uptake of radioactive iodide was 100 per cent. Mere cessation of therapy caused the goiter to disappear rapidly and the uptake to decrease. Para-amino-benzoic and para-amino-salicylic acid and resorcinol ointment are other drugs in this category.

DR. BLAND: Do you think the patient had thyrotoxicosis?

DR. MALOOF: On the basis of the record only, it is dangerous to say.

DR. BLAND: Dr. Maloof thinks he probably did not have thyrotoxicosis! I do not see how I can exclude it; however, patients with much thyrotoxicosis rarely have thrombophlebitis and pulmonary infarcts. Perhaps he had an element of thyrotoxicosis but that certainly played no significant role in his final illness.

Finally we must consider the large liver, which was an outstanding feature from the time it was first noted — a large liver, no swollen neck veins and lungs that do not look to me like those seen with congestive heart failure. Moreover, I think there was no obvious cardiac cause for the persistently large liver. The patient lost only 2 pounds on Mercuhydrin therapy, which further supports the impression that there was probably some other cause for the large liver than simple congestion. There are no liver studies or any discussion in the record about liver disease such as cirrhosis or cancer. Hepatoma may spread to the lungs by way of the blood stream. Metastatic lesions in the lungs usually do not bleed unless there is bronchial erosion or unless the metastatic disease is blood borne in the form of tumor emboli causing infarction. Is that correct?

DR. JOSEPH C. AUB: Yes. Where did the metastatic disease of the lung originate?

DR. BLAND: That is what I am trying to decide; I am considering a hepatoma in this large liver that spread up the venous system directly to the lungs in particles large enough to cause infarcts in the lungs.

In summary I am puzzled about the heart and should like further suggestions. All the evidence points to enlargement of the left ventricle. The history suggests long-standing chronic, relatively mild rheumatic heart disease. The patient surely had pulmonary infarcts either from blood clots or from tumor emboli. The clinicians thought he had infarcts too because they gave him Dicumarol, but apparently refrained from femoral-vein ligation.

In conclusion I suggest that he probably had minimal rheumatic heart disease, though I cannot definitely make such a diagnosis, and that he had pulmonary infarcts. I suspect that he had a malignant lesion, possibly in the liver, and that this was the chief factor in the terminal illness. I do not believe he died of congestive heart failure.

DR. MALOOF: You said you thought he had a minimal amount of rheumatic heart disease.

DR. BLAND: I am not entirely sure that he had rheumatic heart disease.

DR. MALOOF: Could he have had chiefly mitral regurgitation in view of the enlargement and hypertrophy of the left ventricle demonstrated in the electrocardiogram?

DR. BLAND: We are usually quite good in spotting a high degree of mitral regurgitation; such patients usually have an impressive apical systolic murmur.

DR. EARLE M. CHAPMAN: I like Dr. Bland's review and analysis of the situation; that is precisely the way we reasoned. When we were through with this case we were still puzzled in exactly the same way he was. In fact I commented when I first visited the ward that I was not satisfied with the diagnosis of heart disease and heart failure in this case. Indeed, I invited everyone who came on the ward to look at the patient and to tell us what he thought was wrong. This summary of the history in no way reflects the amount of emotional disturbance we experienced in treating this man. I have had many emotional crises over patients, but this one reached the all-time high when we spent an entire luncheon discussing whether or not we should tie the veins in the legs. I believed that the evidence did not favor it, and I was opposed to it because I considered it would be an unnecessary procedure. The house staff insisted that my attitude was entirely unreasonable. We fought it back and

forth; I might read my last note, which I think summarized my opinion in a dispassionate moment:

> I have reviewed the situation and do not agree. There has been no clinical evidence of phlebitis in this case — indeed, the whole situation has been one of relentless heart failure with a rapid rate refractory to digitalis [incidentally, we tried giving too much digitalis as well as too little; the digitalis did not seem to alter the patient's course at all], and the signs at the left base have continued and extended with bloody effusion. This, with the weight loss favors even a possible underlying cancer. The episode of sudden heart failure today, with moist rales over the right lung as well, indicates more heart failure and not another infarct. I think an unnecessary operation should be avoided.

We had the patient on Dicumarol since at first we thought that he had thrombophlebitis. Originally, I believed the infarcts came from the right atrium rather than the leg veins. A patient with cardiac involvement had just died with pulmonary infarcts whose site of origin was proved at autopsy to be the right atrium. With this case fresh in mind, I thought that the emboli in the patient under discussion had originated in the right atrium if they were not malignant.

DR. MALOOF: Why was the myelogram done on this patient?

DR. CHAPMAN: The man had a dilated vein coursing over the right hip, and he also had a hairy, dimpled area in the back. The myelogram was done to show any obstruction in the region of the spina bifida to explain the pain.

DR. BLAND: Will you clear once and for all whether he did or did not have distended neck veins?

DR. CHAPMAN: He did not have.

DR. BLAND: Then he did not have heart failure! But he had a large liver down to the umbilicus. I am still of the school that hates to see people die of what looks like pulmonary infarcts without having had their femoral veins tied.

CLINICAL DIAGNOSES

Multiple pulmonary infarcts.

Phlebothrombosis, deep leg veins.

Rheumatic heart disease, with mitral stenosis.

DR. EDWARD F. BLAND'S DIAGNOSES

Carcinoma, probably primary in liver, with pulmonary metastases.

Cardiac enlargement, ? rheumatic.

Pulmonary infarcts.

ANATOMICAL DIAGNOSES

Oat-cell carcinoma of lung, left lower, with metastases to regional and abdominal lymph nodes, lungs, pericardium, liver, adrenal glands and vertebras.

Pleural effusion, bilateral, sanguineous.

Hemorrhagic bronchopneumonia, right lower lobe.

Pulmonary emphysema, diffuse, severe.

Cardiac hypertrophy and dilatation.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At autopsy the heart was slightly enlarged, weighing about 450 gm.; it was primarily dilated, especially on the right side. The right atrium was the largest chamber; the left atrium was not enlarged. All the valves were normal, and there was no evidence of rheumatic heart disease. The pulmonary artery seemed quite atherosclerotic, suggesting hypertension in the pulmonary circuit. On section the lungs were tremendously emphysematous. Would you say from the roentgenogram, Dr. Hanelin, that that is an emphysematous chest?

DR. HANELIN: I think there is some evidence of emphysema.

DR. CASTLEMAN: In addition to the bullae that were present all along the lung margins and along the apexes, there was a generalized emphysema, the type that may produce right-sided heart failure. I believe the main cause of the enlargement of the heart was the emphysema. There was also some thickening of the endocardium of the left ventricle, which if it had been of a greater degree might perhaps have been called fibroelastosis, a condition about which we do not know too much; however, I doubt if it had much to do with the enlargement of the heart.

The *pièce de résistance* was in the left lower lobe, where a carcinoma infiltrated most of the wall of the bronchus, with extension to the lung parenchyma. All through this lung there were areas of carcinoma surrounding bronchi as well as carcinoma in the hilar areas. This was a rapidly growing oat-cell carcinoma and had metastasized widely. It had extended into the pleura, causing the hemorrhagic fluid on this side. It had metastasized to the liver, which accounted for the enlarged liver, to the vertebras, which perhaps accounted for the pain in the back, and to other areas throughout the body. It had also extended, as these oat-cell carcinomas are likely to do, through the septum of the left lower lobe into the upper lobe, where there was a great deal of disease. There were small tumor areas even in the right upper lobe. There was hemorrhagic bronchopneumonia but no evidence of infarction anywhere. The leg veins were perfectly normal. I do not know what this man had at the age of twenty-seven, when his physician heard a leaky valve, felt a

large liver and noted swollen legs. I am sure it had nothing to do with the present findings.

DR. ALFRED KRANES: Did he have thyrotoxicosis?

DR. CASTLEMAN: He had no evidence of thyrotoxicosis; he had a very small thyroid gland.

DR. HANELIN: Was the liver enlargement primarily due to metastases?

DR. CASTLEMAN: Yes.

DR. BLAND: So he had no congestion.

DR. CASTLEMAN: He had no congestion and your statement — that, when there is a large liver in the absence of distended neck veins one has no right to make a diagnosis of cardiac failure — still holds.

DR. ARTHUR S. PIER, JR.: What caused the fibrillation?

DR. CASTLEMAN: I do not know; can you answer that, Dr. Bland? Could that occur with a right-sided cardiac hypertrophy and emphysema?

DR. BLAND: No; patients with cor pulmonale rarely fibrillate — that is, pure cor pulmonale with lung disease.

DR. CASTLEMAN: There is one finding that may have been the cause of it: the tumor in the left lower lobe had infiltrated the parietal pericardium and had produced nodules on the parietal surface but not on the visceral surface. Could the rubbing there on the visceral surface in any way have caused fibrillation?

DR. BLAND: I think we shall have to assume that the auricular fibrillation was due to infiltration by the carcinoma.

CASE 39412

PRESENTATION OF CASE

A sixty-six-year-old Negress was admitted to the hospital with the chief complaint of back pain.

The patient stated that she had been in excellent health, except for failing vision, until approximately a year before admission. At that time, while in a convalescent home after a recent eye operation, she began to have a severe, nonradiating pain in the lower back that was not associated with cough, dyspnea or hemoptysis but was intensified by motion. There was also a question of a possible pleuritic component, but historical details in this respect were vague. The pain had persisted throughout the entire year, being present most of every day and becoming progressively more severe. Because of the severity of the pain she had had to give up work during the last several months. Various medications prescribed by several physicians gave only partial relief. During the six months before admission she had become aware of somewhat more exertional dyspnea than was usual, along with definite weakness and increased fatigability. In recent months she was accustomed to sleeping in a chair because getting into and out of bed resulted in severe back pain. Orthopnea was denied. Since sleeping in a chair, she had noticed slight pedal edema. For a month before admission she had been complaining of nonradiating substernal pain precipitated by walking. This pain was only fleeting and was allegedly associated with slight dyspnea. She did not believe she had been taking digitalis although she was not sure. She did state that one physician had recently told her that she was hypertensive and had placed her on a low-salt diet. In addition, there had been anorexia and weight loss of unknown degree in the few months before admission. When she was seen at home by her physician a week before admission, she was completely incapacitated by exertional dyspnea but could lie flat in bed without difficulty, the neck veins being enormously distended. The heart displayed a prominent impulse palpable over the pulmonic area. The left ventricle did not appear enlarged. The rhythm was regular at 118, and no gallop was present. A Grade 2 pulmonic systolic murmur was present. The blood pressure was normal. A pronounced friction rub was present over the right lower anterior aspect of the chest, and fine crackles were audible at the right base. There was ++ edema of the legs.

The past history was noncontributory.

Physical examination revealed a well developed, well nourished woman who appeared at least eighty years of age and was quite dyspneic as well as orthopneic. There were corneal scarring and papillary deformity of the right eye secondary to operation. A cataract was present on the left. The fundi could not be visualized. The thoracic spine was markedly kyphotic. There was imperceptible expansion of the chest; no detectable diaphragmatic movement was present. The left cardiac border was percussed 10.0 cm. to the left of the midsternal line. The heart action was described as pounding. The rhythm was regular, and a diastolic gallop was evident. No murmurs were audible. A questionable to-and-fro rub was present. The aortic second sound equaled the pulmonic, and the neck veins were distended and pulsating 4.0 cm. above the clavicles. Crackling inspiratory rales were present at both bases, being more prominent on the right. No pleural friction rub was heard. The abdomen was protuberant and obese, no organs or masses being palpable. There was bilateral costovertebral-angle tenderness. A soft +++ to ++++ pitting edema of both legs was present.

The temperature was 99.6°F., the pulse 110, and the respirations 20 to 25. The blood pressure was 140 systolic, 70 diastolic.

The urine had a specific gravity of 1.010 and gave a ++++ test for albumin; the sediment contained many white cells and an occasional red cell per high-power field. Examination of the blood revealed a hemoglobin of 8.6 gm. per 100 cc. and

a white-cell count of 8900, with 77 per cent neutrophils. The sodium was 136 milliequiv., the potassium 4.7 milliequiv., the chloride 106 milliequiv., and the carbon dioxide 16 milliequiv. per liter; the phosphorus was 5.5 mg., and the nonprotein nitrogen 155 mg. per 100 cc. An electrocardiogram demonstrated prominent Q waves in Leads 1, aVL and V_6 that were interpreted as being suggestive of lateral infarction. X-ray films of the chest and thoracic and lumbar spine revealed enlargement of the heart without characteristic configuration, tortuosity of the aorta, extensive atelectasis of chiefly the lower-lung fields, moderate congestion of the pulmonary vessels, diffuse demineralization of all bones and multiple healed and healing fractures of the ribs.

Upon admission the patient was digitalized, given mercurial diuretics and a low-sodium diet, and placed at absolute bed rest. Within twenty-four hours slight improvement was noted, principally in the degree of dyspnea and orthopnea; however, the improvement was only transitory, and the course from then on was progressively downhill. She continued to have slight backache, and the temperature ranged from 99 to 100.5°F. A second urinalysis showed a specific gravity of 1.010 and gave a ++++ test for albumin. Terminally, she seemed unusually drowsy and had persistent orthopnea, tachypnea and tachycardia. The heart sounds remained unchanged. She died on the fourth hospital day.

Differential Diagnosis

Dr. Joseph C. Aub*: The history and general laboratory studies do not include a good deal of information that I should like to know. I am not told the pH of the urine, whether there was Bence-Jones protein, whether there were plasma cells in the blood smear or what the values of the serum albumin-globulin ratio and alkaline phosphatase were.

Dr. Robert H. Fennell, Jr.: I can add very little; we gave you all the information we had except that the urine had a pH of 5. There was no mention of plasma cells in the differential count.

Dr. Aub: Were there red cells in the urine?

Dr. Fennell: Yes; there was an occasional red cell per high-power field.

Dr. Aub: I do not know whether those were spun urine specimens or not; it makes a good deal of difference.

*Physician, Massachusetts General Hospital.

Since the bones interest me and are probably the reason I was asked to take this case, may I look at the x-ray films now?

Dr. Stanley M. Wyman: In addition to the changes described in the protocol, there are a number of small rarefactions, punched out in character, in the right femur; no definite lesions are present in the left. The skull shows a suggestion of several small, indefinite punched-out rarefactions without any sclerosis around them. In the thoracic spine there are severe compression fractures of all the vertebral bodies. All the bones are markedly demineralized. The chest films demonstrate an enlarged heart, some pulmonary congestion and pleural effusion. The tortuous arteriosclerotic aorta is well seen. The fractures of the ribs can be readily identified.

Dr. Aub: Are there spots in the ribs too?

Dr. Wyman: There may be; it is hard to be sure on a film of this type. This woman was seriously ill, and the films are not ideal.

Dr. Aub: That does not help much.

The patient had uremia and she was sicker of the uremia than she was of the heart condition. She had nitrogen retention and a great deal of protein loss. She had a phosphorus retention and a low carbon dioxide combining power so that she had an acidosis. She was said to have had a high blood pressure, but did not have it when she came into the hospital — I suppose because she was in cardiac failure. She probably had a pericardial friction rub, edema of the lungs and anemia, all of which would go with the uremia. I think she primarily had uremia, with a high nonprotein nitrogen and acidosis, and that means a chronic glomerulonephritis. She also had a large amount of pus in the urine, which makes me wonder whether she did not have a component of pyelonephritis. She had cardiac failure secondary to the uremia. She had arteriosclerosis. The edema of the lungs, the central congestion of the vessels, I think, resulted from both the arteriosclerosis and the uremia. Is that a fair statement? Could the x-ray picture of the chest have been due to uremic edema?

Dr. Wyman: I think so.

Dr. Aub: I suppose that she had a low total protein in the blood stream; no one found that out. Then she had a pericarditis and probably a terminal bronchopneumonia as a safe guess.

The questions are, Why had she the uremia, other than the glomerulonephritis? And, What

was the matter with the bones? I have a choice about those bones. She could have had thin bones from chronic acidosis, a high phosphorus — the syndrome that Albright and Reifenstein[1] described so well, with secondary enlargement of the parathyroid glands. All of this could have been due to renal disease. Secondly, a chronic protein deficiency also tends to cause thin bones because of poor forming of matrix and depletion of protein, so that could have caused the osteoporosis. She could have had this picture as the result of severe nephritis and acidosis.

There is another possibility, one that is puzzling me. Could this have been due to a space-filling defect, a neoplasm that caused the bone picture and the kidney condition? There are two such conditions that could do this; one is multiple myeloma, with which there is an enormous amount of albumin in the urine and bone changes, and the other is hypernephroma. The physicians obviously did not look for Bence-Jones protein, and I do not know what the plasma protein and albumin-globulin ratio were. I do not like the diagnosis of multiple myeloma now after looking at the x-ray films. If she had multiple myeloma involving bones to produce osteoporosis, she ought to have had some large defects in the bones, and there were not any; therefore, I am not going to consider that further, because I do not have the data necessary to make the diagnosis. For hypernephroma, the age is all right; fever may appear early in this disease. The anemia, the osteoporosis and the edema of the legs, which often occurs when the hypernephromatous tissue invades the vena cava, are in favor of that diagnosis. She also had edema elsewhere, but not very much. The liver was not palpable. I cannot see a large liver or kidneys in those films; can you, Dr. Wyman?

Dr. Wyman: No; I think she was breathing when that film was made, and that motion would obscure the visceral outlines. The right kidney is completely outlined and not remarkable; I cannot be sure about the left.

Dr. Aub: This is a diffuse process, which occurs in hypernephroma. Hypernephroma flicks off many emboli that go through the lungs — one does not have to see snowballs — and into the bones. The bones may be loaded with metastases that do not show in the x-ray films; the whole marrow may be replaced with small hypernephromatous masses. The findings in these x-ray films are suggestive of a neoplasm to me, much more so than of osteoporosis due to glomerulonephritis. Yet I have not enough data to make the diagnosis, so I have to rely on the nephritis. If the myeloma or hypernephroma was there, I ought to have been given more data. I do not know what these punched-out areas were; they may have been metastases. I am going to fall back on the comfortable diagnosis of glomerulonephritis and in addition all the conditions I have mentioned as well as a cataract of the eye.

Dr. Farahe Maloof: Do you think hyperparathyroidism could give this picture?

Dr. Aub: I think the patient had enlarged parathyroid glands.

Dr. Maloof: I mean primary hyperparathyroidism.

Dr. Aub: I have no data on which to make that diagnosis. I think this was secondary hyperparathyroidism.

Dr. Arthur S. Pier, Jr.: When I saw this patient at home and sent her into the hospital, I thought the diagnosis was quite obvious. I have learned a great deal from the discussion today. She was an alert Negress who had been having chest pain for about three weeks. The pain had been pleuritic so far as I could make out. I was not impressed by any story of back pain. She was extremely dyspneic; any exertion — getting out of bed or moving to a chair — exhausted her. When she was lying flat she could breathe fairly easily. Her neck veins were distended, and she had moderate edema of the legs. I was impressed by the heart, which showed what I interpreted as marked overactivity of the right ventricle, a pronounced pulmonic second sound and a pronounced thrust of the right ventricle. I did not think she had any gallop. I thought the left ventricle was normal. She had a loud pleural friction rub over the right side of the chest. All the findings seemed to me to add up to multiple pulmonary infarcts over a period of about three weeks, with severe shutdown in the pulmonary circuit and a cor pulmonale. I toyed with the idea of giving her Dicumarol at home. I was puzzled because she had no fever and a normal white-cell count, which were, of course, against a diagnosis of pulmonary infarction. As it was I perhaps fared better than the service, for I did not think she had failure of the left ventricle, but I was about as far off on the diagnosis as one could be.

DR. WYMAN: I would differ with Dr. Aub on the interpretation of the bones and would think of multiple myeloma or perhaps diffuse metastatic carcinoma. Those small, round lesions make me think more of myeloma.

DR. PHILIP H. HENNEMAN: I would take issue with Dr. Aub on two points. If the patient had bone disease with chronic nephritis, it should have been osteitis fibrosa generalisata and not osteoporosis and the x-ray appearance of the bones would have been a bit different. Secondly, I believe that diffuse osteoporosis is a familiar picture in multiple myeloma and one often does not find any "punched-out" areas.

DR. AUB: I should agree with that.

CLINICAL DIAGNOSES

Coronary-artery disease, with myocardial infarction.
Multiple pulmonary emboli.
Osteoporosis.
Uremia.

DR. JOSEPH C. AUB'S DIAGNOSES

Glomerulonephritis, with osteoporosis.
Uremia, with secondary cardiac failure.
Arteriosclerosis.
Bronchopneumonia.

ANATOMICAL DIAGNOSES

Multiple myeloma.
Myeloma kidney.
(Uremia.)
Osteoporosis.
Bronchopneumonia.
Parathyroid adenomas, nonfunctioning.

PATHOLOGICAL DISCUSSION

DR. FENNELL: The extreme fragility of the bones impressed us most at autopsy. The bones were easily broken. One could crush the ribs with the fingers with ease, and the vertebras were very easily cut. Microscopically, in the bone marrow of the vertebras there were small islets of grayish-white, almost mucoid tissue, which had completely replaced the marrow.

The kidneys at the time of autopsy were also impressive; they were of approximately normal size, had smooth surfaces and on section were greasy and rather firm — we would call them lardaceous. On microscopical examination I think one can see at a glance that this is a myeloma kidney (Fig. 1). Almost all the tubules were filled with the eosinophilic hyaline casts. It was a widespread process, but it involved primarily the lower part of the nephron. In some areas there were cells that looked like giant cells, but were probably lining cells of the tubules that encompassed these

FIGURE 1.

masses (Fig. 2). One could look at this and say with fair certainty that this patient had multiple myeloma. A longitudinal section of the rib showed great thinning of the cortex and almost no trabeculae; it had been replaced by sheets of cells resembling plasma cells — a classic case of multiple myeloma.

The heart was amazingly normal; there was no atherosclerosis. The lungs were edematous and

congested and did have some bronchopneumonia, which I think was the terminal feature. There were two small parathyroid adenomas, one in each upper parathyroid gland. The fact that in each gland

FIGURE 2.

there was an adjacent rim of normal tissue, and that the two lower parathyroid glands were normal is evidence that it was not secondary hyperplasia. There was nothing to make us suspect from the anatomic changes that these adenomas were functioning.

DR. HENNEMAN: The concurrence of hyperparathyroidism with Bence-Jones protein in the urine or with multiple myeloma combined with Bence-Jones protein has been described previously,[2] and Dr. Aub and I saw another case of hyperparathyroidism with Bence-Jones protein in the urine in this hospital in 1950.

DR. FENNELL: A post-mortem urine specimen contained Bence-Jones protein.

DR. PIER: Was there any reason for the pleural rub?

DR. FENNELL: The pneumonia was the only cause we found. There was no obvious pleuritis. The patient had many fractured ribs, but we could not find any point where they had punctured into the pleura.

DR. JAMES H. CURRENS: Did you say that the giant cells were tubular cells?

DR. FENNELL: That is the interpretation given to these cells that form masses around the hyaline casts.

DR. CURRENS: Some people attribute them to the Bence-Jones protein.

DR. FENNELL: They are not specific, however. That finding does not mean that the urine of the patient contains Bence-Jones protein.

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PERTINENT SUGGESTION DEPARTMENT

A REPORT has come to hand of an annual survey made of the commercial mail received by a physician engaged in general practice in New York City. It may be assumed that the analysis, covering the four years 1950 through 1953, is representative of the experience of a majority of the practitioners in the country, with the probability that a general practitioner receives more advertising mailings than the specialist.

The subject of the experiment received from May 1, 1952, to April 30, 1953, a total of 3305 direct advertising mailings, an average of precisely 10 each day, or an increase of 10 per cent over the 3021 pieces received in the previous year, and approximately 40 per cent over the 2379 received in 1950. Of this remorseless precipitation 2883 pieces came from pharmaceutical manufacturers, a number that also established a new record. Of the mailings that were received in an envelope, 27 per cent contained a single enclosure, 35 per cent contained two enclosures, and the remainder three or more.

An appeal was made to the physician, in the 3305 bids for his attention, to retain in his consciousness 741 products. Thirty per cent of these, or 229, were new on the market, or at least had never been brought to his attention in this way before. On the other hand, 112 products disappeared, most of them probably never to return, for permanent oblivion usually follows a drop from sight.

An investigation into the types of products considered by their manufacturers and promoters most suitable for such exploitation shows that those used in the treatment of cardiovascular disease have headed the list for three consecutive years — like Ben Adhem's name, they, lo, led all the rest. Antibiotics and sulfonamides came next, with vitamins in third place. Ointments and hematinics have had a private scuffle for fourth place, ointments squeezing through for a victory this year.

To a journalist, such a flood of richly designed and colorful confetti fluttering into the incinerators of the nation has its pathetic aspect. The pity of it, Iago! How much more effective if the ethical products were tastefully displayed in the advertising pages of the substantial medical publications of the world and the rest were encouraged to fold their tents like the Arabs, and as silently steal away!

OSLER'S HUMANITY

AMONG a series of radio talks given by Gilbert Highet,* a native of Glasgow, now a professor of Latin at Columbia University, is a characterization of William Osler, as "a very odd and often very lovable character," dominated from time to time by the Imp of the Perverse. In spite of the chloroform episode, his remarks to the graduating nurses at Hopkins and the antics of his other personality, Egerton Y. Davis, of Caughnawauga, Osler inspired his generation by his delightful essays on his predecessors, designed to show "the world that science is

*Highet, G. *People, Places and Books*. 277 pp. New York: Oxford University Press, 1953.

not a dehumanized activity carried out by calculating machines, but the work of live men devoted to the cause of better life."

No one appreciated literature more than Osler or made the enjoyment of life, humor and friendship a more integral part of his daily occupation. Yet Highet notes a cloud of sadness through his life, abiding in an "angular excitement which is so seldom calm and rich, always so effortful." The air in Osler's home was indeed full of alarms and excursions, a world of telegrams, telephones and messengers; however, he had a magnificent power of detachment, and much was kept from him by devoted secretaries, his admirable wife and a skillful household, alert to mischance or distracting nothings. He could and did wall himself into his own cell and close the windows, like some Carthusian monk, but he always seemed alert to the passerby and quick to throw open the window and explode with a cheery greeting. On the surface life was harmonious but Highet thinks there was "a persistent sour note." The quick step, twinkling eye and gracious manner belied this, muffling the sound that may have rung deep in his consciousness but became no more than a faint murmur to those surrounding him and finding sustenance in his joyful attitude toward his fellow men. He was to his contemporaries, when divorced from the turbulent and slippery field of eager strife and disputation, the universal man, and there was something in him that was without him and remains after him.

TAMING OF THE SHREW

THE Department of Zoology at the University of Wisconsin, long interested in the study of small rodents and comparable fur-bearing mammals, has made notable contributions to existing knowledge on these subjects. Thus investigations have been made into the migratory and mating habits of bats (Order *Chiroptera*) and the eosinophilic indexes of mice (*Mus musculus*), and further valuable researches on the extermination of the undesirable members of the rodent group have cast light on the singularly effective action of Warfarin. The escape mechanism of the lemming (*Lemmus* and *Dicrostonyx*) is said now to be under investigation.

The Department has more recently turned its attention to the smallest of all mammals, the shrew (A. S. *scrēawa*) or shrewmouse. The shrew, defined by Webster as "any of numerous small mouselike mammals (family *Soricidae*), with a long pointed snout, very small eyes and velvety fur," is not to be confused with "a scolding or brawling woman; a termagant," which is quite another and unrelated definition.

About one eighth the size of a mouse and weighing no more than a penny, the longtail shrew has consistently failed to reveal its heart and respiration rates until approached by the Wisconsin biologists. These scientists, by employing a strain gauge, — the same instrument that engineers use in measuring the bending capacity of a steel beam, — have discovered, according to the University of Wisconsin News Service, that the shrew draws about 800 breaths a minute.

With a 4-lead electrocardiogram, the electrodes being placed under the shrew's feet, it was determined that the heart of the shrew contracts from 8 to 21 times a second. From such data it has been estimated that the shrew metabolizes food at the rate of 3 times its weight daily.

A timid creature, the longtail shrew is apparently not of the type so widely publicized by the bard of Avon.

TELEVISION PROGRAMS ON CANCER

A PHENOMENON of contemporary life is the increasing use of television, not only for entertainment but also as a medium for teaching purposes. In keeping with this trend is a special series of thirty television programs, sponsored by the American Cancer Society in co-operation with its Massachusetts Division and the Columbia Broadcasting System. This series, which is designed specifically for physicians, will originate at Columbia — Presbyterian Medical Center and the Memorial Center for Cancer and Allied Diseases in New York City. Since the telecasts will be in color and over a closed circuit, only one outlet can be arranged, and this will be in the auditorium of the Jimmy Fund Building of the Children's Cancer Research Center in Boston. Elsewhere in this issue of the *Journal*, a letter from the president of the Massa-

chusetts Division of the American Cancer Society gives details of the times and dates of the series. The programs will be listed in the notices of Society meetings and conferences in the end pages of the *Journal*.

These programs offer physicians a useful opportunity to watch demonstrations, with discussions by leaders in the field, on nearly every aspect of cancer detection, diagnosis and treatment. Since no reservations or registration fees are required, a large attendance at these interesting and valuable sessions is expected.

Warts are said to be cured by the internal use of carbonate of magnesia.

Boston M. & S. J., *October 12, 1853*

MASSACHUSETTS MEDICAL SOCIETY

APPLICANTS FOR FELLOWSHIP

PUBLISHED IN ACCORDANCE WITH THE PROVISIONS OF CHAPTER V, SECTION 2, OF THE BY-LAWS

BARNSTABLE

ALEXANDER, JAMES KERMOTT, Main Street, Chatham.
Harvard Medical School, 1946.

CALLIS, SIDNEY BERNARD, Main Street, Wellfleet.
Kansas City University College of Physicians & Surgeons, 1937.
Sponsor: Dr. Frank Travers, Barnstable.

COMPTON, ALFRED DONALDSON, JR., 37 Locust Street, Falmouth.
Cornell University Medical College, 1950.

THROPE, ROBERT STEPHEN, 7 Stetson Street, Hyannis.
Tufts College Medical School, 1947.

Lee Britton, M.D., *Secretary*
Bellevue Avenue, So. Yarmouth

BERKSHIRE

BERRY, PAUL NORMAN, 901 West Street, Pittsfield.
University of Vermont Medical School, 1942.

CLIFFORD, THOMAS CARLAW, 17 So. Mountain Road, Pittsfield.
Duke University School of Medicine, 1947.

DAVIS, ROBERT KEAN, Williams College, Williamstown.
Boston University School of Medicine, 1948.

HARRINGTON, FRANCIS JOSEPH, 28 E. Housatonic Street, Pittsfield.
Tufts College Medical School, 1947.

SANDICK, HERBERT, 222 South Street, Pittsfield.
College of Physicians & Surgeons, New York, 1945.

Daniel N. Beers, M.D., *Secretary*
74 North Street, Pittsfield

BRISTOL NORTH

LEWIS, WILLIAM HENRY, 376 Tremont Street, Taunton.
University of Pittsburgh School of Medicine, 1937.

MARKMAN, CHARLES ABRAHAM, 7 No. Main Street, Attleboro.
Tufts College Medical School, 1950.

William M. Downing, M.D., *Secretary*
21 Park Street, Attleboro

BRISTOL SOUTH

BALDWIN, JOSEPH T., 15 Pope Street, New Bedford.
Georgetown University School of Medicine, 1950.

BOYD, JAMES F., JR., Union Hospital, Fall River.
Tufts College Medical School, 1946.

CHERVINSKY, PAUL, 56 Rotch Street, New Bedford.
Tufts College Medical School, 1952.

COMPTON, KENNETH JOHN, 560 Hailes Hill Road, Swansea.
Midwest Medical College, 1938. Sponsor: Dr. Sanford W. Udis, 242 No. Main Street, Fall River.

DEUTCH, MARCELLA G., 321 No. Main Street, Fall River.
Rome University, 1939. Sponsor: Dr. Sydney S. Deutch, 321 No. Main Street, Fall River.

DOUGHERTY, EDWARD FRANCIS, 143 Pebble Street, Fall River.
New York Medical College, 1948.

FLYNN, THOMAS HENRY, 136 Elm Street, So. Dartmouth.
Tufts College Medical School, 1945.

FOX, RAPHAEL P., 325 Whipple Street, Fall River.
Middlesex University School of Medicine, 1931. Sponsor: Dr. Francis Petrone, 140 Winter Street, Fall River.

HALLER, THEODORE HOWES, 180 Elm Street, So. Dartmouth.
University of So. California School of Medicine, 1944.

HIGGINS, THOMAS FRANCIS, 650 Hanover Street, Fall River.
Tufts College Medical School, 1950.

WARREN, ROBERT, 1291 Bedford Street, Fall River.
Hahnemann Medical College, 1946.

James E. Fell, M.D., *Secretary*
173 Purchase Street, Fall River

ESSEX NORTH

ELIAS, WILLIAM SHIBLEY, 281 Haverhill Street, Lawrence.
Tufts College Medical School, 1948.

MALLEN, JOHN KANNAN, 277 Haverhill Street, Lawrence.
Tufts College Medical School, 1947.

SCHISSEL, CHARLES JOSEPH, 168½ Main Street, Amesbury.
Boston University School of Medicine, 1952.

David W. Wallwork, M.D., *Secretary*
5 Third Street, No. Andover

ESSEX SOUTH

BIXBY, FRANK EARL, JR., 1 Monument Square, Beverly.
Cornell University Medical College, 1945.

BREED, ROBERT THOMSON, 45 Nahant Street, Lynn.
Cornell University Medical College, 1948.

CASHMAN, EDWARD L., JR., 96 Puritan Road, Swampscott.
Tufts College Medical School, 1949.

CLARK, WILLIAM JOSEPH, JR., 16 Ocean Street, Lynn.
University of Vermont College of Medicine, 1946.

JEMISON, HOWARD ALLEN, JR., 1 Main Street, Essex.
Bowman Gray School of Medicine, 1951.

MICHELSON, ALAN LAWRENCE, 85 Nahant Street, Lynn.
Jefferson Medical College of Philadelphia, 1948.

ROKOWSKI, WILFRID JOSEPH, Salem Hospital, Salem.
Tufts College Medical School, 1947.

ROSS, DAVID CROMBIE, 156 Lowell Street, Peabody.
University of Edinburgh, Scotland, 1946. Sponsor: Dr. Stanley A. Wilson, Salem Hospital, Salem.

Ever Curtis, M.D., *Secretary*
90 Middle Street, Gloucester

FRANKLIN

GARLAND, MERRITT FREDERICK, JR., 51 Madison Circle, Greenfield.
Tufts College Medical School, 1946.

GIENIS, ALBERT BLAISE, 94 L Street, Turners Falls.
Hahnemann Medical College, 1946.

HARTSHORN, CALVIN WARREN, 9 Linden Avenue, Greenfield.
Tufts College Medical School, 1947.

NOBEL, WERNER NAPHTHALI, 474 Main Street, Greenfield.
University of Basel, Switzerland, 1935. Sponsor: Dr. Milton M. Sisson, 474 Main Street, Greenfield.

Aaron W. Newton, M.D., *Secretary*
Franklin County Public Hospital, Greenfield

HAMPDEN

FOSTER, EDWIN T., 1562 Main Street, Springfield.
St. Louis College of Physicians & Surgeons, 1923. Sponsor: Dr. Eugene Boss, 1537 Main Street, Springfield.

MAKOL, JAMES GEORGE, 167 Maple Street, Springfield.
American University of Beirut, Lebanon, 1943. Sponsor: Dr. George Vassos, Jr., 26 Mulberry Street, Springfield.

SCHIMMEL, MILTON R., 175 State Street, Springfield.
Kansas City University of Physicians & Surgeons, 1944. Sponsor: Dr. George A. Vassos, Jr., 26 Mulberry Street, Springfield.

Allen G. Rice, M.D., *Secretary*
33 School Street, Springfield

HAMPSHIRE

SMITH, FREDRICKA PATCHETT, 264 Elm Street, Northampton.
Columbia University College of Physicians & Surgeons, 1949.

Gordon D. Arnold, M.D., *Secretary*
57 Bridge Street, Northampton

MIDDLESEX EAST

GREEN, THOMAS HENRY, JR., 15 Fielding Street, Wakefield.
Harvard Medical School, 1946.

KENDALL, EDWARD STRONG, 1 Ardley Place, Winchester.
University of Rochester School of Medicine, 1946.

William F. Hickey, Jr., M.D., *Secretary*
15 Dix Street, Winchester

MIDDLESEX SOUTH

ARTER, JAMES CALVIN, 1444 Massachusetts Avenue, Lexington.
Tufts College Medical School, 1952.

IBLEY, LEONARD JONATHAN, 16 Fidelis Way, Brighton.
Boston University School of Medicine, 1952.

ROWELL, WILLIAM MILLER, McLean Hospital, Waverley.
Temple University School of Medicine, 1947.

L BOSQUE, HUGO, Metropolitan State Hospital, Waltham.
National Faculty of Medicine, Mexico, 1944. Sponsor: Dr. Sol Sherman, 1576 Commonwealth Avenue, Boston.

ELMONICO, PETER ALEXANDER, 43 Cross Street, Belmont.
Kansas City University of Physicians & Surgeons, 1943. Sponsor: Dr. Leo Blacklow, 100 Leonard Street, Belmont.

ASCATORE, VINCENT JOHN, 23 Newtonville Avenue, Newton.
Boston University School of Medicine, 1952.

OLDSTEIN, MERRILL MOSES, Middlesex County Sanatorium, Waltham.
Tufts College Medical School, 1948.

AFFEO, ANTHONY JOHN, 20 Hobbs Road, West Medford.
Tufts College Medical School, 1945.

CKART, HARVEY H., 15 Stuart Road, Newton Center.
Middlesex University School of Medicine, 1933. Sponsor: Dr. William A. White, Jr., 270 Commonwealth Avenue, Boston.

AGUIRE, FRANCIS JOSEPH, 1573 Beacon Street, Waban.
Boston University School of Medicine, 1951.

EDYERD, LOUIS ROBERT, 220 Powder House Boulevard, Somerville.
Midwest Medical College, 1934. Sponsor: Dr. John F. McManus, 39 Bay State Road, Boston.

IMETZ, SAMUEL JOSEPH, 84 Grozier Road, Cambridge.
Boston University School of Medicine, 1948.

AW, ROBERT STETSON, 24 O'Rourke Path, Newton Center.
Harvard Medical School, 1945.

VAJIAN, ELI HERMON, 812 Moody Street, Waltham.
Middlesex University School of Medicine, 1943. Sponsor: Dr. Joseph Holmes, 94 Russell Street, Waltham.

LIS, GEORGE JOHN, 28 R Elmwood Street, Somerville.
Boston University School of Medicine, 1950.

TRUE, ROBERT MORAN, 63 Highland Street, Waltham.
University of Vermont College of Medicine, 1952.

WALLER, WILLIAM HENRY, 5 Wallingford Road, Brighton.
University of Georgia School of Medicine, 1948.

Alexander A. Levi, M.D., *Secretary*
481 Beacon Street, Boston

MIDDLESEX WEST

ARBETTER, ALBERT H., 350 Union Avenue, Framingham.
Middlesex University School of Medicine, 1943. Sponsor: Dr. Joseph C. Merriam, 198 Union Avenue, Framingham.

BADIA, LOUIS JAMES, 265 Concord Street, Framingham.
Middlesex University School of Medicine, 1940. Sponsor: Dr. Timothy A. Lamphier, 47 Main Street, Natick.

JOHNSTON, LEICESTER SARGENT, JR., Lake Shore Drive, Cochituate.
Boston University School of Medicine, 1947.

LANGLEY, WARREN FRANKLIN, 154 No. Main Street, Natick.
Boston University School of Medicine, 1951.

LUKERT, RONALD ALLISON, 30 Madden Avenue, Milford.
University of Pennsylvania School of Medicine, 1952.

MORGAN, CHARLES JOSEPH, 83 Main Street, Ashland.
Kansas City University of Physicians & Surgeons, 1943. Sponsor: Dr. Joseph C. Merriam, 198 Union Avenue, Framingham.

RILEY, JAMES THOMAS, 39 E. Central Street, Natick.
University of Vermont College of Medicine, 1951.

SENTER, KENNETH LEE, JR., 4 Dwight Avenue, Natick.
Tufts College Medical School, 1948.

YOUNG, WILLIAM ARTHUR, 2 Strawberry Hill Road, Natick.
University of Toronto Medical School, 1936.

John J. Lepore, M.D., *Secretary*
96 W. Main Street, Marlboro

NORFOLK

ALDEN, JOHN DAVID, 14 Maple Street, Needham.
Tufts College Medical School, 1947.

BEATTY, THOMAS PATRICK, 125 Flaherty Way, So. Boston.
Tufts College Medical School, 1946.

BLAKE, ARNOLD IRVING, 120 Main Street, Peabody.
Boston University School of Medicine, 1950.

CALLAHAN, FRANCIS CHARLES, 20 Bean Court, Roxbury.
Tufts College Medical School, 1950.

CARVER, WALTER DICKINSON, 361 Blue Hill Avenue, Milton.
Boston University School of Medicine, 1950.

CUGELL, DAVID WOLF, 249 River Street, Mattapan.
Long Island College of Medicine, 1947.

DAWBER, THOMAS ROYLE, 39 Sheridan Road, Wellesley Hills.
Harvard Medical School, 1937.

DAY, MAX, 591 Morton Street, Dorchester.
University of Toronto, 1947.

FARRELL, GEORGE EDWARD, JR., 16 Penhallow Street, Dorchester.
Tufts College Medical School, 1948.

GRIFE, HARRY EDWARD, 367 Harvard Street, Brookline.
Tufts College Medical School, 1934.

HAMOLSKY, MILTON WILLIAM, 16 Moville Street, W. Roxbury.
Harvard Medical School, 1946.

HARRIS, ABRAHAM J., 729 Washington Street, Brookline.
Midwest Medical College, 1934. Sponsor: Dr. Jacob Chayet, 1807 Beacon Street, Brookline.

HENZER, DORA, 72 Rawson Road, Brookline.
University of Manitoba, Winnipeg, 1943.

HERSHMAN, HYMAN A., 11 Capen Street, Dorchester.
Hahnemann Medical College, 1949.

JOHNSON, ROBERT STANISLAUS, JR., 591 Morton Street, Dorchester.
Albany Medical College, 1945.

KAUFMAN, DAVID, 80 Bellingham Road, Chestnut Hill.
Boston University School of Medicine, 1947.

LAYTON, M. LEWIS, 137 Columbia Road, Dorchester.
Middlesex University School of Medicine, 1931. Sponsor: Dr. Philip S. Foisie, 520 Commonwealth Avenue, Boston.

LEACH, GEORGE VINCENT, 375 Jerusalem Road, Cohasset.
College of Physicians & Surgeons, Boston, 1929. Sponsor: Dr. Francis J. Wenzler, 449 River Street, Mattapan.

LONG, ROBERT THOMAS, 591 Morton Street, Dorchester.
Columbia University College of Physicians & Surgeons, 1945.

MARKS, LEON JOSEPH, V. A. Hospital, So. Huntington Avenue, Boston.
Johns Hopkins University School of Medicine, 1948.

PEREDNIA, WILLIAM PETER, 52 Prospect Street, Norwood.
Tufts College Medical School, 1951.

RYAN, VINCENT PAUL, 14 Winslow Road, Sharon.
Tufts College Medical School, 1950.

SANDIFER, MYRON GUY, JR., 6 Ridgefield Road, Cochituate.
Harvard Medical School, 1947.

SILVERMAN, HERBERT RALPH, 1141 Beacon Street, Brookline.
University of Virginia Department of Medicine, 1946.

SMITH, ARTHUR KENT, 208 So. Huntington Avenue, Boston.
Tufts College Medical School, 1950.

SWARTZ, ABRAHAM, 12 Gurney Street, Boston.
Middlesex University School of Medicine, 1945. Sponsor: Dr. Maurice H. Shulman, 416 Marlboro Street, Boston.

TURCOTTE, RODOLPH HARVEY, Medfield State Hospital, Harding.
Boston University School of Medicine, 1947.

WELLS, ROE EDWIN, JR., 30 Payne Road, Newton Highlands.
Cornell University Medical College, 1946.

WESSLING, PHILIP IGNATIUS, 528 Weld Street, W. Roxbury.
Boston University School of Medicine, 1948.

WHITE, LEMOYNE, 29 Hilltop Road, Chestnut Hill.
Harvard Medical School, 1940.

WINTER, WILLIAM DAVID, JR., 122 Edgewood Road, Westwood.
Harvard Medical School, 1947.

Solomon L. Skvirsky, M.D., *Secretary*
277 State House, Boston

NORFOLK SOUTH

FENTIN, EDWARD, 3 Lunt Street, Quincy.
Middlesex University School of Medicine, 1932. Sponsor: Dr. Isadore Schwartz, 1079 Hancock Street, Quincy.

HAYES, JOHN STEPHEN, 18 Thayer Street, Quincy.
Tufts College Medical School, 1946.

SCERRY, ROBERT THOMAS, 109 No. Main Street, Cohasset.
Yale University School of Medicine, 1950.

STREET, RUSSELL BARBER, JR., 114 Whitwell Street, Quincy.
University of Maryland School of Medicine, 1945.

Herman S. Beal, M.D., *Secretary*
4 Richmond Street, Weymouth

SUFFOLK

ADELIZZI, DANTE LOUIS, 31 Wordsworth Street, E. Boston.
Kansas City University of Physicians and Surgeons, 1943. Sponsor: Dr. A. Paul Der Hagopian, 39 Cary Avenue, Chelsea.

BARGAR, HAROLD M., 520 Beacon Street, Boston.
Tufts College Medical School, 1947.

BEHRINGER, GLENN EWING, 266 Beacon Street, Boston.
Harvard Medical School, 1945.

BENECCHI, LEO PAUL, 25 Hyde Street, Revere.
Middlesex University School of Medicine, 1945. Sponsor: Dr. Harry Silverman, 137 Shirley Avenue, Revere.

D'ANGIO, GIULIO JOHN, 818 Harrison Avenue, Boston.
Harvard Medical School, 1945.

DAVIDOW, ERNEST PAUL, 368 Longwood Avenue, Boston.
Tufts College Medical School, 1950.

ETSCOVITZ, ELI A., 236 Independence Drive, Chestnut Hill.
Tufts College Medical School, 1948.

FARRELL, ROBERT J., 26 Logan Way, South Boston.
Tufts College Medical School, 1948.

GARDELLA, JOSEPH WARREN, Mass. General Hospital, Boston.
Johns Hopkins University School of Medicine, 1944.

HAMMOND, JAMES BICKNELL, 118 Mason Terrace, Brookline.
University of Utah School of Medicine, 1945.

HENNEMAN, PHILIP HARRY, 18 Cushing Road, Brookline.
Harvard Medical School, 1946.

KETCHUM, WILLIAM FRANCIS, 501 Boylston Street, Boston.
Harvard Medical School, 1944.

KRALL, LEO PAUL, 45 Riverglen Road, Wellesley.
College of Medical Evangelists, 1943.

LAZERTE, GORDON D., 153 Oakley Road, Belmont.
Tufts College Medical School, 1948.

LEVINE, MILTON, 1543 No. Shore Road, Revere.
Middlesex University School of Medicine, 1937. Sponsor: Dr. Louis Siegel, 72 Shirley Avenue, Revere.

McGOVERN, JOSEPH JAMES, 829 Beacon Street, Boston.
Georgetown University School of Medicine, 1951.

O'CONNOR, ROBERT BRENDAN, 175 Berkeley Street, Boston.
Harvard Medical School, 1939.

PAINTER, PAUL HAWLEY, Mass. General Hospital, Boston.
St. Louis University School of Medicine, 1947.

REGAN, CHARLES DOUGLASS JAMES, 520 Commonwealth Avenue, Boston.
Harvard Medical School, 1946.

SABBATH, JOSEPH CONRAD, 636 Beacon Street, Boston.
McGill University, 1947.

SELVIG, HOWARD STANLEY, 38 Beacon Street, Boston.
University of Minnesota Medical School, 1942.

SISSON, WARREN RICHARDS, JR., 818 Harrison Avenue, Boston.
Syracuse University College of Medicine, 1945.

SMITH, TAYLOR ROBERT, 243 Charles Street, Boston.
University of So. California School of Medicine, 1944.

STANDER, ALVIN VICTOR, 382 Commonwealth Avenue, Boston.
University of Lausanne, 1940. Sponsor: Dr. David Landau, 31 Bay State Road, Boston.

SWATEK, WILLIAM CYRIL, 37 Bennet Street, Boston.
College of Medical Evangelists, 1949.

VALIN, ROBERT JOHN, 270 Commonwealth Avenue, Boston.
University of Pittsburgh School of Medicine, 1946.

Charles G. Shedd, M.D., *Secretary*
1180 Beacon Street, Brookline

WORCESTER

BRODEUR, NORMAND EDWARD, 2 Slater Street, Webster.
Laval University Faculty of Medicine, 1946.

HARRIS, JEFFREY HOPE, Harvard Common, Harvard.
Boston University School of Medicine, 1950.

HAY, RICHARD CARMAN, 85 Lovell Road, Holden.
University of Vermont College of Medicine, 1946. Transfer from Grafton County Medical Society, Hanover, N. H.

JOHNSON, ROBERT ANDREW, 137 Richmond Avenue, Worcester.
Albany Medical College, 1940.

KELLY, ROBERT FRANCIS, 74 Jacques Avenue, Worcester.
Tufts College Medical School, 1948.

MORIARTY, DAVID MICHAEL, 305 Belmont Street, Worcester.
Boston University School of Medicine, 1947.

OAKLEY, DOROTHY HELEN WARNECKE, 5 Alexander Avenue, Clinton.
University of Wisconsin Medical School, 1949. Transfer from Wisconsin State Medical Society.

RICE, EARLE WINSLOW, 12 Regent Street, Worcester.
University of Vermont School of Medicine, 1949.

ROY, CHARLES ARTHUR, 134 Everett Street, Southbridge.
Tufts College Medical School, 1947.

TOMAIOLO, PASQUALE PETER, 265 Turnpike Road, Shrewsbury.
College of Physicians and Surgeons, Boston, 1944. Sponsor: Dr. Edmond Croce, 340 Main Street, Worcester.

UHL, HENRY STEPHEN MAGRAW, 89 Forest Street, Worcester.
Harvard Medical School, 1947. Transfer from the Michigan State Medical Society.

WEIDEMANN, KARL CHRISTIAN, 3 Bayberry Road, Worcester.
University of Frankfurt, 1944. Sponsor: Dr. Elwood O. Horne, 36 Pleasant Street, Worcester.

WYLIE, HOWARD LEE, 10 Phillips Drive, Worcester.
University of Chicago School of Medicine, 1945.

Paul F. Bergin, M.D., *Secretary*
57 Cedar Street, Worcester

WORCESTER NORTH

ANDES, T. EUGENE, Gardner State Hospital, Gardner.
Temple University Medical School, 1940.

Seymour I. Nathanson, M.D., *Secretary*
882 Main Street, Fitchburg

CORRESPONDENCE

APPLICATIONS FOR SOCIETY MEMBERSHIP

To the Editor: I thought it might be of interest to send you the enclosed tabulation, which you may consider worthy of publication. The figures were obtained from applications of physicians applying for membership in the Massachusetts Medical Society that had accumulated during the twenty-five years that I have been secretary of the Middlesex South District Medical Society. The tabulation does not include every physician who has applied during these years. The graduates from unapproved medical schools were omitted, and a small number of unavailable applications from those who graduated from Class A schools could not be considered.

I am not certain that any particular conclusion can be drawn. I can only say that the figures demonstrate a cross-section for the Middlesex South District Medical Society, one of nineteen districts of the Massachusetts Medical Society.

ALEXANDER A. LEVI, M.D.

Boston

The following information was obtained from applications presented by graduate physicians to the Middlesex South District Medical Society for membership in the Massachusetts Medical Society and covers the years indicated.

Boston University School of Medicine: available information dates to 1931 and includes graduates from the colleges listed below, through 1942.
Assumption College: 1
Boston College: 1
Boston University: 4
Brown University: 2
Cornell University: 1
Dartmouth College: 2
Fordham University: 1
Hamilton College: 1
Harvard University: 5
Holy Cross College: 1
Lehigh University: 1
Massachusetts State College: 1
Tufts College: 4
University of Massachusetts: 2
University of Vermont: 1
University of Wisconsin: 1
Yale University: 1

Columbia University College of Physicians and Surgeons: earliest graduate from college (below) in this group, 1925; latest, 1940.
Brown University: 1
Dartmouth College: 1
Harvard University: 1
Tufts College: 1
Yale University: 1

Harvard Medical School: earliest date of graduation from college (below), 1931; latest year of college graduation, 1942.
Boston College: 1
Bowdoin College: 2
Brown University: 1
Columbia University: 2
Dartmouth College: 1
Harvard University: 19
Haverford College: 1
Holy Cross College: 2
Princeton University: 1
Tufts College: 1
University of Colorado: 1
University of Florida: 1
University of Michigan: 1
University of North Dakota: 1
University of Rochester: 1
University of Virginia: 2
Westminster College: 1
Williams College: 3
Yale University: 5

Tufts College Medical School: earliest year of graduation from college (below), 1933; latest date of graduation from college, 1942.
Bates College: 1
Boston College: 18
Boston University: 1
Brown University: 1
Clark University: 1
Colby College: 1
Dartmouth College: 2
Harvard University: 15
Holy Cross College: 4
Jackson College: 1
Louisiana College: 1
Massachusetts Institute of Technology: 1
Massachusetts State College: 1
Radcliffe College: 1
Regis College: 1
Springfield College: 1
Tufts College: 13
University of Maine: 1
University of New Hampshire: 2
Vanderbilt College: 1
Yale University: 1

Yale University School of Medicine: earliest date of graduation from college (below), 1933; latest date of graduation from college, 1940.
Boston College: 1
Bowdoin College: 1
Columbia University: 1
Harvard University: 2
Massachusetts Institute of Technology: 1
Radcliffe College: 1
Tufts College: 1
University of Washington: 1
Wellesley College: 1
Yale University: 4

TELEVISION PROGRAMS ON CANCER

To the Editor: Although a printed flyer has been sent to all physicians, I am anxious to call the profession's attention again to the color television programs on cancer to be shown beginning October 21 from 5 to 6 p.m. in the auditorium of the Children's Cancer Research Center (the Jimmy Fund Building), 35 Binney Street, Boston. The first four programs with the subjects, speakers and dates, are as follows:

October 21. Cancer in Medical Practice. Drs. Alfred Gellhorn, Morton Levin and Maurice Root.

November 4. The Significance of Cough. Dr. George Humphreys.

November 18. Prostatic Cancer. Dr. Perry Hudson.

December 2. Gastric Ulcer. Drs. Milton Porter and Charles Flood.

These telecasts will originate in the Columbia—Presbyterian Medical Center and the Memorial Cancer Center in New York and will be shown on closed circuit by CBS initially in Boston, New York, Philadelphia, Pittsburgh and Toledo. The programs have been made available to physicians by the American Cancer Society in co-operation with the Columbia Broadcasting System and the Massachusetts Division of the American Cancer Society.

Of the thirty programs to be telecast, the first four are to be shown bi-weekly. After December 2 a program will be shown each Wednesday from 5 to 6 p.m. in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston.

Physicians from all over New England are invited. No fees, and no registration or reservations are required.

GEORGE R. DUNLOP, M.D., *President*
American Cancer Society (Massachusetts Division), Inc.

Boston

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Anzeige und Ausführung der Eingriffe an Ohr, Nase und Hals. By Walther Uffenorde. Second revised and supplementary edition by Doz. Dr. med. Hellmut Uffenorde, chief physician,

Hals-Nasen-Ohrenabteilung des Krankenhauses Alt-Mariahilf, Göttingen. With a supplementary contribution, *Die Eingriffe zur Gehörverbesserung*. By Prof. Dr. med. Horst Wullstein, chief physician, Hals-Nasen-Ohrenabteilung des Jung-Stilling-Krankenhauses, Siegen (Westf.). 8°, cloth, 540 pp., with 408 illustrations. Stuttgart: Georg Thieme, 1952. DM 79.80. (Distributed by Grune and Stratton, New York.)

The first edition of this book on surgery of the ear, nose and throat was issued in 1942 by the elder Uffenorde, who died in 1947. The new edition has been revised by his son, Hellmut. It is a typical, comprehensive, well organized German textbook. Dr. Wullstein, in a short chapter, discusses operations for impaired hearing. It is a practical book, without reference to the literature. There is a good index, and the publishing is excellent. The book should be in all collections on the subject.

NOTICES

ANNOUNCEMENT

Dr. Robert J. Fahey announces the removal of his office from 23 Bay State Road, Boston, to 314 Commonwealth Avenue, Boston, and 175 Washington Street, Winchester, in association with Dr. Joseph J. O'Connor for the practice of internal medicine.

SOUTH END MEDICAL CLUB

The regular monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on Tuesday, October 20, at 12 noon. Dr. John R. Graham, chief, Medical Service, Faulkner Hospital, and clinical associate in medicine, Massachusetts General Hospital, will speak on the subject "Migraine."

All physicians are cordially invited to attend.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Tuesday, October 20, at 8:15 p.m. The following program will be presented by the departments of Neurology, Neurosurgery and Psychiatry of the Massachusetts General Hospital, Dr. Stanley Cobb presiding:

Psychiatric Aspects of Low-Back Pain. John C. Nemiah, M.D.

A Comparison of the Activity of Various Defined Fractions of Bovine White Matter in the Production of Experimental Allergic Encephalomyelitis in Rabbits. Byron H. Waksman, M.D., Huntington Porter, M.D., Marjorie D. Lees, A.B., and Raymond D. Adams, M.D.

External Localization of Brain Tumors Using Automatic Scanning and Positron Emitting Isotopes of Arsenic. Gordon L. Brownell, Ph.D., and William H. Sweet, M.D.

FIFTH CONFERENCE ON ALCOHOLISM

The Fifth Conference on Alcoholism, sponsored by the Boston Committee on Alcoholism, will be held in John Hancock Hall, Boston, on Wednesday, October 21, from 2 to 10 p.m. The program will include an address by Dr. Samuel B. Kirkwood, Massachusetts Commissioner of Public Health, lectures and a panel discussion.

Reservations ($1 for the session and $4.50 for the dinner) may be made with the Boston Committee on Alcoholism, 419 Boylston Street, Boston (telephone, KEnmore 6-1954 or KEnmore 6-4284).

GRANTS FOR RESEARCH IN CARDIOVASCULAR DISEASE

The Research Allocations Committee of the Massachusetts Heart Association will consider requests from institutions for grants-in-aid from the fund that the Association will have available for research in cardiovascular diseases during 1953–54.

The Committee will meet on the following dates during the current academic year: November 13, January 8, March 5, April 2, May 7 and June 4. To be placed on the agenda for any given meeting, applications should be in the hands of the Committee at least two weeks in advance of the meeting. Requests received after the deadline will be placed on the agenda of the next meeting.

Applicants should telephone or write to the Massachusetts Heart Association, 650 Beacon Street, Boston 15 (COpley 7-4400), for a copy of the detailed instructions, before preparing their applications.

PHI DELTA EPSILON GRADUATE CLUB OF BOSTON

The first meeting of the Phi Delta Epsilon Graduate Club of Boston will be held at the Hotel Beaconsfield, Brookline, on Wednesday, October 28. The meeting will be a cocktail and dinner meeting (cocktails from 6:30 to 7:30 and dinner at 7:30 p.m.). The speaker of the evening will be Mr. Al Capp, the peripatetic cartoonist and author. A business meeting will precede the cocktail hour.

FRIED LECTURES

The first annual Fried Lecture will be held in the Usen Auditorium, Newton-Wellesley Hospital, at 8:30 p.m. in October and November. The dates and subjects are as follows:

October 19. Hormonal Factors in the Managem...t of Malignant Disease. Dr. J. Hartwell Harrison, urologic surgeon, Peter Bent Brigham Hospital, and associate clinical professor of genitourinary surgery, Harvard Medical School

October 26. The Diagnosis of Adrenal Insufficiency and Cushing's Syndrome. Dr. George W. Thorn, physician-in-chief, Peter Bent Brigham Hospital, and Hersey Professor of the Theory and Practice of Physic, Harvard Medical School

November 2. Extrapelvic Aspects of Gynecologic Conditions. Dr. Somers H. Sturgis, surgeon in gynecology, Peter Bent Brigham Hospital, and associate clinical professor of gynecology, Harvard Medical School.

November 9. The Use of ACTH and Cortisone. Dr. George W. Thorn.

Physicians and medical students are invited to attend.

HAMPDEN DISTRICT MEDICAL SOCIETY

A meeting of the Hampden District Medical Society will be held jointly with the Woman's Auxiliary at the Roger Smith Hotel, Holyoke, on Tuesday, October 27, at 6 p.m.

MIDDLESEX SOUTH WOMAN'S AUXILIARY

A luncheon and fashion show will be sponsored by the Woman's Auxiliary to the Middlesex South District Medical Society at the Meadows, Framingham, on Tuesday, October 20, at 1 p.m.

SOCIETY MEETINGS AND CONFERENCES

October 12–14. National Gastroenterological Association. Page 266, issue of August 6.

October 12–14. Medical and Dental Military Symposium. Page 470, issue of September 10.

October 12–17. Seventh International Congress of Pediatrics. Page 170, issue of July 23.

October 13. New York Society for Circulatory Diseases. Page 50, issue of September 17.

October 14. New England Cardiovascular Society. Page 546, issue of September 24.

October 14–December 2. Course in child psychiatry (pediatric neuropsychiatry). Page 428, issue of September 3.

October 15 and 16. New England Tuberculosis Conference. Hotel Bradford, Boston.

October 15–17. Annual Course in Postgraduate Gastroenterology. Page 260, issue of August 6.

October 16. New England Society of Anesthesiologists. Page 428, issue of September 3.

October 17–20. American Association of Blood Banks. Page 112, issue of June 25.

October 19 and 26, November 2 and 9. Fried Lectures. Notice above.

October 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

October 19–December 21. Hartford Medical Society Program. Page 260, issue of August 6.

October 20. Harvard Medical Society. Notice above.

October 20. South End Medical Club. Notice above.

October 20. Middlesex South Woman's Auxiliary. Notice above.

October 21. Fifth Conference on Alcoholism. Notice above.

October 21–23. International Symposium on Virus Infections. Page 546, issue of September 24.

October 23 and 24. Eastern Section of American Trudeau Society. Page 506, issue of September 17.

October 25–29. American Institute of Dental Medicine. Page 12, issue of July 16.

October 27. Hampden District Medical Society. Notice above.

October 28. Phi Delta Epsilon Graduate Club of Boston. Notice above.

October 29. New England Obstetrical and Gynecological Society.

November 2–4. New England Postgraduate Assembly. Hotel Statler, Boston. Page ii.

(*Notices concluded on page xvii*)